Synopsis for study EGF104900

Name of finished products: TYVERB® 250mg Filmtabletten

Name of active substances: Lapatinib

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Personal identifiable data of investigators (investigator names) are not published in this report, as consent according to Section 4a of the German Federal Act on Data Protection is not available for any of the investigators.

Synopsis

Study Number: EGF104900

Title: A Randomized, Multicenter, Open-Label, Phase III Study of Lapatinib in Combination with Trastuzumab versus Lapatinib Monotherapy in Subjects with Metastatic Breast Cancer whose Disease has Progressed on a Trastuzumab-Containing Regimen.

Investigator(s):

Study center(s): Eighty-eight (88) centers in 13 countries (Austria [2 centers], Bulgaria [1], Canada [1], Croatia [1], Czech Republic [3], Finland [1], Germany [13], Greece [3], Italy [4], Poland [3], Spain [4], United Kingdom [3], and United States of America [49]).

Publication(s):

Blackwell K, Burstein HJ, Storniolo AM, et al. Randomized study of lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. J Clin Oncol 2010;28:1124-30.

Wu Y, Amonkar MM, Sherill BH, et al. Impact of lapatinib plus trastuzumab versus single-agent lapatinib on quality of life of patients with trastuzumab-refractory HER2+ metastatic breast cancer. Ann Oncol 2011;22:2582-90.

Study Period: 17 November 2005 (first subject first visit) - 29 October 2010 (last subject last visit).

Phase of Development: III

Objectives:

Primary: The primary objective of the study was to evaluate and compare the antitumor activity, in terms of progression-free survival (PFS), of trastuzumab plus lapatinib versus lapatinib monotherapy in subjects with HER2 gene amplified metastatic breast cancer (MBC).

Secondary:

- Evaluate and compare the two treatment groups with respect to the following: overall survival (OS), tumor response rate (complete or partial), clinical benefit (complete response, partial response or stable disease for at least 6 months), time to response and duration of response.
- Determine the qualitative and quantitative toxicities associated with oral lapatinib administered daily in combination with trastuzumab versus lapatinib monotherapy.

- Compare baseline and on treatment serum concentrations of human epidermal growth factor receptor 1 (HER1) and human epidermal growth factor receptor 2 (HER2) extracellular domains (ECDs), potentially perform proteomic analysis to detect other shed tumor proteins, identify changes in the protein profile and correlate to treatment response.
- Characterize the subject population by determination of intratumoral expression of HER1, HER2, and downstream biomarkers which may help elucidate the effects of lapatinib on the target and other proteins along relevant pathways in the tyrosine kinase pathway.
- Evaluate quality of life (QOL) status within the study population and compare the impact on QOL between treatment groups.
- Exploratory evaluation of pharmacogenetic (PGx) variants and/or tolerability of study treatments
- Exploratory evaluation of PGx variants and efficacy
- Proteomic analysis will be performed on plasma samples taken at specified visits to identify changes in the protein profile that are associated with response to treatments.

This updated abbreviated clinical study report (ACSR) presents results for OS (with a mature dataset), safety and the biomarker objectives. PFS data have not been updated as they were mature at the time of the previous clinical study report (CSR). Results of exploratory pharmacogenetic and proteomic analyses will be reported separately.

Results for the other study objectives are provided in the previous CSR [GlaxoSmithKline Document GM2007/00059/00]. Endpoints reported in the previous CSR include: PFS, interim OS, overall tumor response rate, clinical benefit response (CBR) rate, time to response, duration of response, health outcomes and interim safety data (clinical cut-off date of 29 June 2007).

In this end-of-study ACSR, the cutoff for the OS analyses was 23 January 2009, which was when sufficient events had occurred to provide a mature dataset. Last subject last visit was on 29 October 2010, and the final database lock occurred on 5 May 2011. The following cut-off dates were used in this report:

Updated Information	**Data cut-off date**
Subject disposition	29 October 2010
Final OS	23 January 2009
Post-disease progression treatments and their impact on final OS analysis	23 January 2009
Final cumulative safety analyses	29 October 2010
Narratives for serious adverse events (SAE) and adverse events (AE) leading to withdrawal	29 October 2010

Methodology:

This was a global, randomized, multicenter, open-label Phase III study in subjects with HER2-positive MBC whose disease had progressed on a trastuzumab-containing regimen. Subjects were randomized (1:1) to either the combination treatment arm (lapatinib plus trastuzumab) or the monotherapy arm (lapatinib alone).

Subjects randomized to lapatinib monotherapy who experienced objective disease progression (by radiological imaging and/or photography) after receiving at least 4 weeks of treatment could opt to crossover to receive lapatinib plus trastuzumab. This crossover option was included in the study design to provide these subjects access to dual-HER2 blockade treatment following disease progression.

Subjects were followed from the time that they discontinued study treatment (randomized therapy or crossover therapy if applicable) for any reason other than death. Subjects who withdrew from study treatment without disease progression received a tumor response evaluation (until objective disease progression or start of new anticancer therapy) in the follow-up assessments. Subjects were followed until death, study closure (if sooner) or when OS data on the study population had matured (i.e., when approximately 75% of subjects regardless of arm died) and a final OS analysis would be performed (per protocol).

Number of subjects:

Planned: 270 subjects

Enrolled and analyzed: 296 subjects

Diagnosis and main criteria for inclusion: Subjects were women, at least 18 years of age, with histologically or cytologically confirmed Stage IV HER2-positive MBC, who had an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 2 and left ventricular ejection fraction within institutional normal range. The most recent regimen was required to have contained trastuzumab, either alone or in combination with other therapy in the metastatic setting, and each subject's disease must have progressed while on this regimen. Eligible subjects had bone only disease or at least one measurable lesion, as defined by Response Evaluation Criteria in Solid Tumors 1.0 (RECIST 1.0).

Treatment administration:

Drug	Dosage	Time for Administration
Combination arm		
Lapatinib	1000 mg (4 tablets)	Daily; approximately the same time of day each day, preferably either at least 1 hour before or 1 hour after breakfast
Trastuzumab loading dose[a]/Day 1	4 mg/kg IV infusion	Approximately 90 minutes on Day 1
Trastuzumab subsequent therapy	2 mg/kg IV infusion[b]	Approximately 30 minutes weekly
Monotherapy arm		
Lapatinib	1500 mg (6 tablets)	Daily; approximately the same time of day each day, preferably either at least 1 hour before or 1 hour after breakfast

Abbreviation: IV=Intravenous.

a. If subjects were already receiving treatment with trastuzumab at the time of study entry then a loading dose did not need to be administered.

b. Subjects remaining on study therapy at Week 108 and beyond may have received trastuzumab either at 2 mg/kg weekly or at 6 mg/kg at 3 week intervals (q3-weekly) according to the discretion of the investigator

Batch numbers used: R408055, R321106, R359703, R323020, R257932, R257943, R239947, R226829, R199432, R212693, R212690, R212676, R212681, 041038125, R212683, R199438, 041037395, 041037389, 041037394, 041037396.

Criteria for evaluation: Efficacy endpoints discussed in this ACSR are: pre-defined OS and subgroup analysis of OS (all based on the 23 January 2009 cut-off date). Cumulative safety information are also presented, which comprise: AEs, clinical laboratory evaluations (hematology and clinical chemistry), vital signs, electrocardiogram and echocardiogram / multigated acquisition scans.

Exploratory analysis of serum epidermal growth factor receptor (EGFR) and HER2 ECDs and gene expression analysis using ribonucleic acid (RNA) isolated from subjects' archived formalin-fixed, paraffin-embedded (FFPE) tumor tissue are also presented in this report. The purpose of these exploratory analyses is to identify biomarker relationships with the treatment effects of lapatinib as a monotherapy and in combination with trastuzumab to develop biological hypotheses for further consideration.

Statistical methods:

Efficacy analysis used the Intent-to-Treat (ITT) Population, which included all subjects randomized to the study irrespective of whether or not study treatment was received and was according to the treatment to which they were randomized. Of the 296 subjects in the ITT Population, 5 subjects did not have hormone receptor status (estrogen receptor and/or progesterone receptor) verified in the case report form (CRF) data. Therefore the data for these subjects were excluded in any efficacy analyses adjusted for stratification factors. These analyses used the pre-defined stratified analyses described, but are based on the 'ITT Population with Strata' and were considered to be the primary analyses. ITT analyses (with all randomized subjects) were also provided for supportive purposes, and were based on the unverified strata provided through the Interactive Voice Response System.

OS was summarized using Kaplan-Meier curves, compared between treatment arms using a stratified log-rank test, and included subgroup analyses.

Exploratory analyses of PFS using a stratified log-rank test were also performed for the ITT population to compare the treatment effect in subjects according to their baseline serum HER2 ECD levels.

Exploratory analyses of PFS and OS using proportional hazards regression models were performed on the ITT population using gene expression data derived from subject's archival FFPE tumor tissue. False discovery rate (FDR) was used for multiplicity correction. These analyses used the same data cut-off dates as used for determination of the primary endpoint (PFS) and the mature OS.

Demographics:

A total of 296 female subjects were enrolled in this study at 88 study centers. Subjects had a median age of 51.0 years and most subjects were white (94%). The study population was heavily pre-treated, had an overall poor prognosis, and the median time from diagnosis of Stage IV disease to study entry equal to 2 years.

Most subjects had visceral disease (73%) and the median number of prior trastuzumab-containing regimens in the metastatic setting was three. In addition, 150 subjects (51%) in the study population were estrogen receptor negative and progesterone receptor negative. Trastuzumab had been received by 178 (60%) subjects less than 1 month prior to screening.

Efficacy Results:

The pre-defined final OS analysis (data cut-off date 23 January 2009) included 291 subjects per their randomized treatment, regardless of crossover status. In the ITT Population (excluding 5 subjects without CRF verified hormone receptor status), a total of 218 subjects (75%) had died (105 [72%] in the combination arm and 113 [78%] in the monotherapy arm). The median OS in the ITT Population was 14 months for the combination arm and 9.5 months for monotherapy arm (Hazard ratio [HR]: 0.74; 95% confidence interval [CI]: 0.57, 0.97; stratified log rank p=0.026). There was a 10% improvement in absolute OS rate at 6 months and a 15% improvement at 12 months for subjects who received combination treatment compared with subjects who received monotherapy treatment.

Exploratory analyses support the overall OS benefit from combination therapy, as OS was consistent in the majority of the subgroups analyzed.

At the time of the cut-off for the pre-specified OS analysis (23 January 2009), 60 (78%) of the 77 subjects who crossed over to combination therapy had died. The median OS in these subjects was 10.8 months (95% CI: 8.7, 15.6).

Safety Results: The safety profile was similar to that reported in the previous CSR [GlaxoSmithKline Document Number GM2007/00059/00]. Across both treatment arms the most common AEs (in >15% of subjects in either treatment arm) were diarrhea, nausea, rash, vomiting, and fatigue.

Most AEs were Grade 1 or Grade 2. The most commonly reported Grade 3 AE for both treatment arms was diarrhea (11 subjects [7%] in the combination arm; 10 subjects [7%] in the monotherapy arm). Overall, 218 subjects (113 subjects [76%] in the combination arm; 105 subjects [72%] in the monotherapy arm) had AEs that were treatment-related. One subject (<1%) in the combination arm had Grade 4 diarrhea. No Grade 4 AEs were reported for the monotherapy arm. A total of 64 subjects (40 subjects [27%] in the combination arm and 24 subjects [16%] in the monotherapy arm) experienced SAEs. The protocol specified additional criteria for describing a limited range of expected events as an SAE regardless of grade. Consistent with this, the majority of SAEs were ejection fraction decreases, reported in 7 subjects (5%) in the combination arm, and 1 subject (<1%) in the monotherapy arm. No other SAE was reported by more than 3% of subjects in either arm.

There were no additional fatal SAEs reported since the previous CSR. Six subjects had died due to an AE at the previous CSR cut-off date. Three subjects (2%) in the combination arm died due to AEs of cardiac failure and pulmonary embolism (one subject), respiratory failure (one subject) and sepsis (one subject). The event of cardiac failure was considered treatment-related by the investigator. Two subjects (1%) died in the monotherapy arm due to AEs of hepatic failure and renal failure (one subject), and internal injury (one subject). One subject who crossed over to combination therapy died due to an AE of respiratory failure.

A total of 26 subjects in the randomized phase (16 subjects [11%] in the combination arm and 10 subjects [6%] in the monotherapy arm) discontinued from study treatment due to AEs. The most commonly reported AEs leading to discontinuation of study treatment in more than 1 subject were increased blood bilirubin, headache and thrombocytopenia in the combination arm; and fatigue and diarrhea in the monotherapy arm.

Fifty-four subjects (70%) who crossed over to combination therapy reported AEs. The most frequent AEs (reported for more than 10% of subjects) in subjects who crossed over to combination therapy were diarrhea (in 15 subjects, 19%), fatigue (in 15 subjects, 19%), nausea (in 13 subjects, 17%), anemia (in 9 subjects, 12%), and cough (in 9 subjects, 12%). The maximum severity of most AEs reported for subjects who crossed over to combination therapy was Grade 1 or Grade 2. Thirteen subjects (17%) reported Grade 3 events, and no Grade 4 or Grade 5 events were reported for more than 1 subject. Thirty-one subjects (40%) had AEs that were treatment-related, and 6 subjects (8%) withdrew from the study due to an AE. SAEs were reported for 10 subjects (13%) who received combination treatment after crossover from monotherapy. The protocol specified additional criteria for describing a limited range of expected events as an SAE regardless of grade. Consistent with this, ejection fraction decrease was observed to be the most frequently reported SAE (in 3 subjects, 4%); although, in 2 subjects the ejection fraction decrease was clinically asymptomatic. No other SAE was reported by more than one subject.

Cardiac, pulmonary (pneumonitis), and rash events are known class effect toxicities of agents that target the EGFR and/or HER2 receptors. In addition, diarrhea and hepatobiliary events have been reported for small molecule tyrosine kinase inhibitors. As such, further analyses were performed to understand the characteristics of these events.

More subjects in the combination arm (11 subjects, 7%) than the monotherapy arm (3 subjects, 2%) reported at least 1 cardiac event (comprising reported AEs with the preferred term of ejection fraction decrease, left ventricular dysfunction, cardiac failure, and myocardial infarction). In these subjects, most of the events (64% in the combination arm and 67% in the monotherapy arm) experienced were Grade 1 or 2 in severity. Asymptomatic cardiac events occurred in 10 of the 11 subjects in the combination arm, and in 2 of 3 subjects in the monotherapy arm and symptomatic cardiac events occurred in 3 subjects in the combination arm and 1 subject in monotherapy arm. Overall, 9 events (64%) in the combination arm and all 3 events (100%) in the monotherapy arm resolved, with all left venricular ejection fraction (LVEF) values returning to near or above the institutional lower limit of normal (In the combination arm; 7 of the asymptomatic events resolved and the 4 events reported as unresolved were due to follow-up LVEF assessments not performed (2 subjects had subsequent disease progression, 1 subject discontinued study treatment and 1 subject withdrew from the study). In the combination arm, 2 symptomatic events resolved and one was fatal.

More subjects in the combination arm (92 subjects, 62%) experienced diarrhea compared with subjects in the monotherapy arm (70 subjects, 48%). The majority of subjects in both treatment arms experienced diarrhea events that were Grade 1 or 2 in severity. Five diarrhea events, including 2 in the combination arm and 3 in the monotherapy arm were considered serious. Diarrhea events led to the withdrawal of 2 subjects (both in the monotherapy arm) from the study. The majority of diarrhea events in both treatment arms resolved without the need for a dose modification.

Fewer subjects in the combination arm (35 subjects, 23%) experienced rash compared with subjects in the monotherapy arm (43 subjects, 29%). All but one subject experienced rash events that were Grade 1 or 2 in severity; one subject in the monotherapy arm experienced a Grade 3 rash event. However, none of the rash events in either treatment arm were considered serious, and none of the rash events led to withdrawal of a subject from the study. The majority of rash events in both treatment arms resolved without the need for a dose modification.

A similar proportion of subjects in the combination arm (16 subjects, 11%) experienced hepatobiliary events (i.e. events reported as an AE) compared with subjects in the monotherapy arm (13 subjects, 9%). Laboratory abnormalities comprised the majority of hepatobiliary AEs. Six subjects in the combination therapy arm and 5 subjects in the monotherapy arm experienced Grade 3 or 4 hepatobiliary events; one event in each arm was considered treatment-related per investigator. There were fewer hepatobiliary SAEs in the combination arm (1 subject, 2%) compared with the monotherapy arm (4 subjects, 17%). There was one fatal SAE of hepatic failure. This event was considered to be unrelated to treatment by the investigator, and the cause of death was reported as disease under study. Hepatobiliary AEs that led to permanent discontinuation of study treatment were similar between the combination arm (6 events, 13%) and the monotherapy arm (3

events, 13%). The majority (62%) of the hepatobiliary events in the combination arm resolved, whereas 54% of the hepatobiliary events in the monotherapy arm did not resolve. In addition, no subjects had liver function test values which met Hy's law criteria (alanine aminotransferase [ALT] ≥3 x upper limit of normal (ULN) and total bilirubin ≥2.0 x ULN, with normal alkaline phosphatase (ALP).

No events of pneumonitis were reported in either the combination arm or the monotherapy arm. A Grade 2 event of pneumonitis was reported for 1 subject (1%) who crossed over to combination treatment. This subject was <65 years, and the event was not considered serious or related to treatment. The event subsequently resolved without a dose reduction or discontinuation of study treatment.

Biomarker Results:

Exploratory baseline serum HER2 ECD analyses showed that subjects with baseline HER2 ECD greater than 15 ng/mL experienced longer PFS during combination therapy than during monotherapy (HR: 0.55; 95% CI: 0.40, 0.76; median PFS: 15.9 weeks compared with 8.3 weeks). PFS was similar in subjects with baseline HER 2 ECD levels of 15 ng/mL or lower (HR: 0.93; 95% CI: 0.60, 1.42; median PFS: 10.0 weeks compared with 8.0 weeks).

Previous analyses of serum EGFR ECD levels from other studies in the lapatinib clinical program showed no significant associations between serum EGFR levels and response to lapatinib. Consequently, EGFR ECD results were not further analyzed with efficacy endpoints.

In the exploratory analyses to identify genes that were differentially expressed between treatment arms, no genes met the FDR significance threshold of ≤0.05, therefore the treatment arms were combined for further gene expression analysis. The results from these analyses demonstrated that subjects with tumors exhibiting high HER2 expression levels and low matrix metalloprotease 7 (MMP-7) expression levels experienced significantly longer PFS. There were no genes significantly associated with OS (FDR adjusted p-value >0.05).

Conclusions:

- A clinically relevant improvement in OS was observed in the combination arm.
    - The median 4.5 months overall survival advantage with combination treatment compared with monotherapy treatment is similar to improvements seen with the addition of trastuzumab to chemotherapy in first-line HER2-positive MBC. This survival benefit was observed in a population of subjects whose HER2-positive MBC progressed on prior trastuzumab-based regimens.
- OS analyses demonstrated significant reductions of relative risk for the combination treatment compared with monotherapy treatment.

- An acceptable tolerability and safety profile was observed in subjects with MBC, during lapatinib treatment in combination with trastuzumab. The safety profile was consistent with the results reported in the previous CSR as well as with the established safety profile of each agent without evidence of a new safety signal for the combination. Consistent with a chemotherapy-free regimen, a low level of hematological toxicity was observed for the combination. The majority of cardiac events were asymptomatic and resolved without dose modification enabling continued treatment on study. This is recognizing that as protocol specified, the majority, although asymptomatic, were considered to be SAEs, and were reported during routine LVEF assessments.
- The combination of lapatinib with trastuzumab had a favorable benefit/risk ratio in this population as treatment of HER2-positive MBC. Therefore, these results support a dual HER2-targeted, chemotherapy-free treatment strategy in patients previously treated with trastuzumab.

Date of Report: February 2012

Synopsis

Identifier: GM2007/00059/00 **Study Number:** EGF104900

Title: A randomized, multicenter, open-label Phase III study of lapatinib in combination with trastuzumab versus lapatinib monotherapy in subjects with metastatic breast cancer whose disease has progressed on a trastuzumab-containing regimen

Investigator(s): This was a multicenter study.

Study center(s): This study was carried out at 88 centers in 13 countries (Austria [2 centers], Bulgaria [1], Canada [1], Croatia [1], Czech Republic [3], Finland [1], Germany [13], Greece [3], Italy [4], Poland [3], Spain [4], United Kingdom [3], and United States of America [49]).

Publication(s): J Clin Oncol; 26, 2008 (abstract 1015).

Study Period: The first subject was enrolled on 17 November 2005. The data cut off date for this study was 29 June 2007; 19 subjects were continuing treatment at the time of reporting.

Phase of Development: III

Objectives: The primary objective of the study was to evaluate and compare the antitumor activity, in terms of progression-free survival (PFS), of trastuzumab (Herceptin®) plus lapatinib (TYKERB™/TYVERB™) versus lapatinib monotherapy in subjects with ErbB2 (human epidermal growth factor receptor 2 [HER2]) gene amplified[1] metastatic breast cancer (MBC).

The secondary objectives were to:

- Evaluate and compare the two treatment groups with respect to the following: overall survival (OS), tumor response rate (complete or partial), clinical benefit (complete response [CR], partial response [PR] or stable disease [SD] for at least 6 months), time to response and duration of response
- Determine the qualitative and quantitative toxicities associated with oral lapatinib administered daily in combination with trastuzumab versus lapatinib monotherapy
- Compare baseline and on treatment serum concentrations of the epidermal growth factor receptor (EGFR [ErbB1]) and ErbB2 extracellular domains, potentially perform proteomic analysis to detect other shed tumor proteins, identify changes in the protein profile and correlate to treatment response

[1] To be eligible for this study, subjects had to have documented amplification of the ErbB2 gene by fluorescence in situ hybridization (FISH), or, documented overexpression of the ErbB2 protein by immunohistochemistry (IHC) in primary or metastatic tumor tissue (i.e., have a tumor positive for ErbB2).

- Characterize the subject population by determination of intratumoral expression of ErbB1, ErbB2, and downstream biomarkers which may help elucidate the effects of lapatinib on the target and other proteins along relevant pathways in the tyrosine kinase pathway
- Evaluate quality of life (QOL) status within the study population and compare the impact on QOL between treatment groups

The pharmacogenetic (PGx) research objectives were to investigate the relationship between genetic variants and safety and/or tolerability of study treatments and the relationship between genetic variants and efficacy of study treatments if high variability in responses were observed.

Proteomic analyses could have been performed on plasma samples taken at specified visits to identify changes in the protein profile that were associated with response to study treatments.

Methodology: This was a randomized, open label, Phase III study to evaluate and compare the safety and efficacy of lapatinib in combination with trastuzumab (hereafter referred to as the combination arm or combination treatment) compared with lapatinib monotherapy (hereafter referred to as the monotherapy arm or monotherapy treatment) in subjects with MBC. Subjects were randomized to receive either oral lapatinib 1000 mg once daily plus trastuzumab 4 mg/kg administered as an intravenous (IV) loading dose, followed by 2 mg/kg IV weekly, or oral lapatinib 1500 mg once daily.

Subjects who had objective disease progression after receiving at least 4 weeks of treatment with lapatinib monotherapy were eligible to crossover to combination therapy (subjects then enrolled in the Crossover Population). These subjects received combination treatment of trastuzumab plus lapatinib until further disease progression was observed, they withdrew from study treatment due to unacceptable toxicity or the subject withdrew their consent.

Number of subjects:

	Number (%) of subjects		
	Combination arm (N=148)	Monotherapy arm (N=148)	All Subjects (N=296)
Status			
Completed study[a]	52 (35)	66 (45)	118 (40)
Prematurely withdrawn from study	14 (9)	17 (11)	31 (10)
Ongoing[b]	82 (55)	65 (44)	147 (50)
Reason for withdrawal from study			
Subject consent withdrawn	5 (3)	7 (5)	12 (4)
Death[c]	4 (3)	4 (3)	8 (3)
Lost to follow-up	2 (1)	5 (3)	7 (2)
Investigator decision	2 (1)	0	2 (<1)
Other[d]	1 (<1)	1 (<1)	2 (<1)

a. Subjects were considered to have completed the study if they died and were not considered to have been prematurely withdrawn from the study.
b. No date of completion was available for these subjects at the time of data analysis, as these subjects were being followed for survival or were on study treatment, and so are listed as ongoing in the study. Thirteen subjects were receiving combination treatment (8 subjects from the combination arm and 5 subjects who had opted to crossover to combination treatment at the time of disease progression) and 6 subjects were receiving monotherapy treatment.
c. Classified as withdrawn from study in error. Subjects were considered to have completed the study if they died.
d. One subject had an SAE in the combination arm and 1 subject reported an AE in the monotherapy arm.

Diagnosis and main criteria for inclusion: For inclusion in this stud subjects had to meet the following criteria: subjects were non-pregnant females who were using adequate contraception and aged ≥18 years. They had histologically/cytologically confirmed MBC with Stage IV disease, which had progressed on regimens containing an anthracycline and a taxane in either the adjuvant or metastatic setting. Subjects had documented progression following at least one trastuzumab plus cytotoxic chemotherapy or antihormonal therapy regimen in the metastatic setting. The most recent regimen must have included trastuzumab, either alone or in combination with other therapy in the metastatic setting, and subjects must have progressed while on this regimen. Archived tumor tissue was available for testing and subjects had documented amplification of the ErbB2 gene by FISH or documented overexpression of the ErbB2 protein by IHC. Subjects had at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) or bone only disease. Subjects had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and adequate hematological and organ function (i.e., renal, hepatic, and cardiac function). Subjects who did not meet any of these criteria were reported as protocol violators.

Treatment administration: Subjects were randomized to receive either:

- Oral lapatinib 1000 mg daily plus trastuzumab 4 mg/kg administered as an IV loading dose, followed by 2 mg/kg IV weekly; or
- Oral lapatinib 1500 mg daily

The following batch numbers of lapatinib tablets were used in this study: 041037389, 041037394, 041037395, 041037396, 041038125, R199432, R199438, R212676, R212681, R212683, R212690, R212693, R226829, and R239947.

Criteria for evaluation: The primary efficacy endpoint was PFS, defined as the time from randomization until the first documented sign of disease progression or death due to any cause.

The secondary efficacy endpoints were: OS; overall tumor response rate (confirmed CR or PR) determined by radiologic evaluation according to RECIST; clinical benefit response rate (confirmed CR or PR at any time or SD for at least 24 weeks [6 months]); time to response; duration of response; time to progression (TTP)[2]; and QOL as assessed by the Functional Assessment of Cancer Therapy-Breast questionnaire (Version 4, 1997).

The incidence, toxicity and causality of adverse events (AEs), serious adverse events (SAEs), and other safety parameters were also assessed. Safety assessments included AEs, clinical laboratory evaluations, vital signs, electrocardiograms (ECGs), echocardiogram (ECHO) or multigated acquisition (MUGA) scans, ECOG performance status, and body weight.

Serum samples for ErbB1 and ErbB2 enzyme-linked immunosorbent assay assays were collected; these samples could also be used for potential proteomic analysis. A blood sample was taken for PGx assessments from subjects who consented.

Statistical methods: Randomization was stratified by hormone receptor status and visceral/nonvisceral disease. The RECIST guidelines were used to assess clinical activity and disease status. Both investigator and independent reviewer assessments were reported. The primary efficacy endpoint was investigator evaluated PFS. Supporting data for the primary endpoint were provided by independent evaluation of PFS.

PFS and OS were summarized using Kaplan-Meier curves and compared between treatment arms using a stratified log-rank test. The Pike estimator of the treatment hazard ratio (HR) based on the log-rank test was provided, together with a 95% confidence interval (CI). The Kaplan-Meier estimates for median PFS, median OS, and the first and third quartiles were presented with approximate 95% CIs. Greenwood's formula was used to calculate the standard error of the estimates from the Kaplan-Meier curve.

Exact 95% CIs were calculated for the overall tumor response rate and clinical benefit response rate. Nonstratified exact 95% CIs and stratified Fisher's exact tests were calculated for the difference in overall tumor response rates and clinical benefit response rates between treatment arms. Zelen's test for homogeneity of the odds ratios across all strata were performed as a measure of validation.

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[2] TTP was included in the protocol as an endpoint and was defined as the interval between the date of randomization and the earlier of date of disease progression or death due to breast cancer. However, TTP is confounded by death due to other causes and is similar to PFS, therefore, only PFS was examined.

Summary:

Demographics

A total of 296 female subjects were enrolled in this study at 88 study centers. Subjects had a median age of 51.0 years and most subjects were white (94%). The study population had an overall poor prognosis, with the median time from diagnosis of Stage IV disease to study entry equal to 2 years.

Most subjects had visceral disease (73%) and the median number of prior trastuzumab-containing regimens in the metastatic setting was three. In addition, the majority of subjects in the study population were estrogen receptor negative and progesterone receptor negative (150 [51%] subjects overall). A total of 197 (67%) subjects had ErbB2 3+ status by IHC and 253 (85%) had positive ErbB2 status by FISH. Trastuzumab had been received by 178 (60%) subjects less than 1 month prior to screening.

Efficacy

Primary endpoint

Median PFS was longer in subjects who received combination treatment (12.0 weeks and 16.4 weeks) compared with subjects who received monotherapy treatment (8.1 weeks and 11.1 weeks) by investigator and independent evaluation, respectively. The difference between the treatment arms for PFS was statistically significant in favor of the combination arm (HR of 0.73 [95% CI: 0.57, 0.93; p-value 0.008] and HR of 0.71 [95% CI: 0.52, 0.98; p-value 0.027], by investigator and independent evaluation respectively).

Based on investigator assessment, in the 73 subjects who decided upon progression to crossover to the combination arm, median PFS was 6.9 weeks (95% CI: 4.1, 8.1).

Secondary endpoints

Overall tumor response rate was higher in the combination arm (10.3% and 6.2%) compared with the monotherapy arm (6.9% and 2.8%) by investigator and independent evaluation, respectively. However, the difference between the two treatment arms was not statistically significant. Following crossover to combination treatment, overall tumor response rate was 2.7% (95% CI: 0.3, 9.5) by both investigator and independent evaluation.

Similarly, investigator and independently evaluated clinical benefit response rate was higher in the combination arm (24.7% and 18.5%, respectively) compared with the monotherapy arm (12.4% and 9.0%, respectively). This was despite these subjects having entered the study with breast cancer, that had progressed on a median of three prior trastuzumab-containing regimens in the metastatic setting and a median of six prior anticancer therapies overall. The difference in clinical benefit response rate between the two treatment arms was statistically significant by both investigator (odds ratio: 2.2; 95% CI: 1.2, 4.5; p=0.01) and independent evaluation (odds ratio: 2.2; 95% CI: 1.0, 4.9; p=0.04). Clinical benefit response rates were the same for subjects based on

investigator and independent evaluation of tumor response following crossover from monotherapy to combination treatment (8.2% [95% CI: 3.1, 17.0]).

In total, 57 (39%) subjects in the combination arm and 71 (48%) subjects in the monotherapy arm died as of the data cut off date (Intent-to-treat Population). There was a trend for improved OS in the combination arm (median 51.6 weeks) compared with the monotherapy arm (39.0 weeks) (HR: 0.75; 95% CI: 0.53, 1.07; p=0.106). In the Crossover Population, 31 (42%) subjects had died as of the data cut off date. The Kaplan-Meier estimate for median OS was 41.4 weeks (95% CI: 34.6, 70.0) for subjects who crossed over to combination treatment compared with 38.9 weeks (95% CI: 28.0, 52.1) for those subjects who did not crossover after progression on monotherapy treatment.

There were too few subjects experiencing a confirmed CR or PR to analyze time to response or duration of response.

Safety

Lapatinib in combination with trastuzumab or as monotherapy had an acceptable tolerability and safety profile, despite subjects having breast cancer that had progressed after treatment with a median of five prior cytotoxic regimens. The overall incidence of AEs and AE toxicity grades were consistent with the known safety profiles for lapatinib and trastuzumab.

The most commonly reported AE in both treatment arms of the Safety Population was diarrhea. Diarrhea was reported more frequently in the combination arm than in the monotherapy arm. The difference between the treatment arms may be attributed to the number of Grade 1 and Grade 2 events; the incidence of Grade 3 and Grade 4 events was similar in both treatment arms. The higher incidence in the combination arm may also be due to the overlapping toxicities of lapatinib and trastuzumab. Nausea, rash, and fatigue and vomiting were also frequently reported in both treatment arms. Most events resolved without the need for dose modification and the majority were National Cancer Institute common terminology criteria for AEs Grade 1 or Grade 2 in toxicity. A higher incidence of rash was reported in the monotherapy arm, this is thought to be due to the higher dose of lapatinib received by these subjects. The table below summarizes AEs of special interest, which are monitored closely throughout the lapatinib program.

Adverse Events of Special Interest in Either Treatment Arm of the Safety Population and Following Crossover Regardless of Relationship

AEs of special interest	Number (%) Subjects		
	Safety population		Crossover population
	Combination arm (N=149)	Monotherapy arm (N=146)	(N=73)
Decreased left ventricular ejection fraction[a]	9 (6)	3 (2)	2 (3)
Diarrhea[b]	90 (60)	70 (48)	13 (18)
Rash[c]	33 (22)	43 (29)	4 (5)
Hepatobiliary events[d]	3 (2)	6 (4)	1 (1)
Interstitial pneumonitis	0	0	1 (1)[e]

a. Includes the terms: ejection fraction decrease, left ventricular dysfunction, cardiac failure, and myocardial infarction. There was a slight increased incidence of asymptomatic decreases of LVEF in the combination arm (5 events) compared with the monotherapy arm (2 events). In addition, 2 subjects each presented with an event of decreased LVEF following crossover to combination treatment; both events were considered asymptomatic. However, most AEs which presented with decreased LVEF were Grade 1 or Grade 2.
b. Includes the terms: diarrhea, loose stools, and frequent bowel movements.
c. Includes the terms: acne, dermatitis, eczema, erythema, folliculitis, rash, rash papular, and rash pustular.
d. No hepatobiliary event was reported for more than 2 subjects and all except 2 subjects had entered the study with liver metastases or had a history of liver masses.
e. The event resolved, was not considered to be related to treatment or to be an SAE, and did not lead to a dose change or discontinuation of study treatment.

Six subjects had fatal AEs (3 subjects in the combination arm and 2 subjects in the monotherapy arm, and 1 subject following crossover to combination therapy). Only one of these events (cardiac failure), in a subject who received combination treatment, was considered by the investigator to be treatment related and possibly due to disease progression. Cause of death for this subject was reported as cardiac insufficiency and an unconfirmed pulmonary thromboembolism.

More subjects in the combination arm (22%) compared with the monotherapy arm (16%) had SAEs. The most commonly reported SAEs were events which presented with decreased left ventricular ejection fraction (LVEF) (8 [5%] subjects) and dehydration (4 [3%] subjects) in the combination arm, and diarrhea (3 [2%] subjects) and events which presented with decreased LVEF (3 [2%] subjects) in the monotherapy arm.

Twenty-six subjects were discontinued from study treatment due to AEs. Adverse events leading to discontinuation were reported more frequently in the combination arm (17 [11%] subjects) compared with the monotherapy arm (9 [6%] subjects).

The AEs reported following crossover to combination treatment were in general consistent with those reported in the Safety Population. However, the incidence of the following AEs was lower by more than 10% following crossover compared with the incidence in the Safety Population: diarrhea (18% and 54%, respectively), nausea (15% and 28%, respectively), and rash (5% and 26%, respectively). As observed in more advanced cancer, anemia was reported more frequently following crossover compared with the incidence in the Safety Population (12% and 3%, respectively). Five [7%]

subjects had an AE leading to discontinuation and 8 [11%] subjects each had a single SAE while receiving combination treatment during the crossover period of the study.

The hematological and clinical chemistry abnormalities reported during the study were reflective of subjects with MBC and consistent with the established safety profile of lapatinib. The majority of subjects had normal vital signs, ECG, and ECHO/MUGA scans during the study. As to be expected in a population of this type, ECOG performance status deteriorated during the study.

Quality of Life

A comparison of QOL summary scores, in terms of change from baseline, revealed no statistically significant difference between the combination and monotherapy treatment arms. The two treatment arms also appear to be numerically similar, suggesting that QOL may be similar for subjects receiving combination treatment and for subjects receiving monotherapy treatment in this heavily pretreated population.

Conclusions: The combination of lapatinib and trastuzumab prolonged PFS and improved the clinical benefit response rate for subjects with relapsed ErbB2 positive MBC over treatment with lapatinib alone. A trend for improved OS was also observed in subjects receiving combination treatment. Modest activity was observed with lapatinib monotherapy in this heavily pretreated population of MBC subjects. No worsening of QOL was observed for subjects receiving combination treatment compared with those receiving monotherapy. Both treatment regimens had an acceptable safety profile. The overall incidence of AEs and AE toxicity grades were consistent with the known safety profiles for lapatinib and trastuzumab. Thus, lapatinib in combination with trastuzumab offers a chemotherapy-free option, which imparts a clinical benefit to subjects with advanced ErbB2 positive MBC, whose disease has progressed on or after multiple lines of prior trastuzumab-based therapy.

Date of Report: 10 September 2008

Appendix 1 to Synopsis for study EGF104900

Overview of pharmacogenetic and proteomic analyses results

(pooled analysis of 947 lapatinib treated subjects obtained from 12 different EGF lapatinib clinical trials, including EGF104900)

EGF113892

Title: PGx240 lapatinib liver safety pharmacogenetics in EGF10023, EGF103892, EGF20009, EGF103009, EGF102580, EGF100151, EGF30001, EGF104900, EGF105764, EGF104383, EGF105084, and VEG20007

Date of Report: 23rd April 2009 (Study Completed)

Objective

The objective of this exploratory pharmacogenetic study was to investigate whether the selected genetic variants were associated with the on-treatment ALT and TBL elevations observed within these studies.

Methodology

The RAP provides a detailed description of the statistical analyses used for this investigation. The two phenotypes that were evaluated were maximum on-treatment liver chemistry values for ALT and TBL with respect to the upper limit of normal. These phenotypes were evaluated separately in case-control and quantitative trait analyses and jointly in a combined case-control analysis. ALT and TBL cases were defined as maximum on-treatment elevations of ≥3xULN and ≥1.5xULN, respectively, and control subjects were defined as maximum on-treatment ALT or TBL of ≤1xULN. Approximately 950 patients with an adequate, fully consented DNA sample had available clinical data for these phenotypes. After subject genotyping quality control was completed, a total of 947 patients remained for pharmacogenetic analyses on at least one genetic variant. Due to difference in the incidence of ALT elevations when compared with other treatments, lapatinib-pazopanib combination-treated patients from VEG20007 were excluded from this primary analysis.

A candidate gene approach of approximately 300 genes was utilised, which included the following: 1) Twenty five genes, selected based lapatinib mechanism pathway and ADME: (*CYP*, *UGT* and drug transporter) genes. 2) As genetic understanding of drug-induced liver injury is limited, a comprehensive drug induced liver injury (DILI) panel, developed by GSK in consultation with external liver experts was also evaluated. This DILI panel is comprised of approximately 6500 single nucleotide polymorphisms (SNPs) in 270 gene regions derived from the postulated mechanisms involved in the pathophysiology of DILI. In both approaches, genetic variation in each gene region was investigated using tag SNPs selected from the International HapMap project and/or high density SNP coverage consisting of all functional SNPs with a previously recorded genotype to phenotype correlation. 3) *HLA* genes (4-digit genotypes of *HLA-A, -B, -C, -DPB1, -DQA, -DQB1,* and *-DRB1,* 2-digit genotypes of *–DRB3, -DRB4* and *–DRB5*) were also evaluated since published examples have implicated an immune component in liver injury caused by other drugs. Evaluation of HLA genes focussed on a subset of the total number of patients consisting of all ALT cases (N=47) and matched controls (N=47).

Results

For the TBL phenotype, 125 variants from 66 gene regions were significantly ($p<0.01$) associated with TBL elevation by QTA (N~900) and/or case-control analyses (~60 cases and ~395 controls). Thirty-one of these variants were from one gene region, the *UGT1A@* cluster. A key result was the association of the Gilbert's syndrome variant UGT1A1*28 with

TBL elevation, significant for both QTA ($1.25x10^{-5}$, n=899) and case (N=60) and control (N=396) analysis ($p=1.04x10^{-5}$). Thirty five percent of TBL cases were TA7/TA7 genotype and 82% of TBL cases had at least one TA7 allele, compared to 5% and 48% respectively for controls. Patients homozygous for the *UGT1A1**28 variant had an odds ratio (95%CI) of 10.7 (5.3-21.6) of being a case than a control, when compared to the other genotypes.

For the ALT phenotype, 51 variants from 34 gene regions were significantly ($p<0.01$) associated with ALT elevation by QTA (n~900) and/or case-control analyses (~35 cases and ~285 controls). In the HLA analysis, two genetic signals were significantly associated ($p<0.05$) with ALT elevation in matched case-control analysis (47 cases and 47 controls): HLA-DRB1*0701 (along with other HLA variants correlated with this allele) and HLA-B*4403. HLA-DRB1*0701 was significantly associated with ALT elevation (p=0.014), with an odds ratio (95%CI) of 4.4 (1.6-12.0) for HLA-DRB1*0701 carriage compared to all other observed HLA-DRB1 alleles. One ALT case had the HLA-DRB1*0701/*0701 genotype and 40% of ALT cases had at least one copy of the HLA-DRB1*0701 allele, compared to none and 13% respectively for controls. HLA-B*4403 was significantly associated with ALT elevation (p=0.033), with an odds ratio (95%CI) of 4.0 (1.1-14.3) for HLA-B*4403 carriage compared to all other observed HLA-B alleles. Twenty three percent of ALT cases carried one copy of the HLA-B*4403 allele (no subjects were observed to carry two copies), compared to 6% respectively for controls.

For combined ALT and TBL cases, 20 variants from 15 gene regions were significantly ($p<0.01$) associated the combined case-control endpoint (~9 cases and ~225 controls). For key markers, 5/13 combined ALT/TBL cases were UGT1A1*28 TA7/TA7 homozygotes (38%) and 4/13 combined ALT/TBL cases had at least one of the significant HLA alleles discussed above (31%).

These results are considered exploratory and will require follow-up in additional independent clinical datasets to enable replication and validation. At this stage, these results are not useful for clinical application.

Date of Report: April 2009

Appendix 2 to Synopsis for study EGF104900

Overview of Protocol Amendments

Excerpt from protocol including final amendment version 3
dated 21-DEC-2009

Division: Worldwide Development
Retention Category: GRS019
Information Type: Protocol Amendment

Title:	A Randomized, Multicenter, Open-Label, Phase III Study of Lapatinib in Combination with Trastuzumab versus Lapatinib Monotherapy in Subjects with Metastatic Breast Cancer whose disease has progressed on a Trastuzumab-Containing Regimen

Compound Number: GW572016

Effective Date: 21-DEC-2009

Protocol Amendment Number: 03

Description:

This is a randomized, open-label phase III study to evaluate and compare the safety and efficacy of lapatinib in combination with trastuzumab versus lapatinib monotherapy in subjects with metastatic breast cancer. Eligible subjects must have a confirmed diagnosis of metastatic breast cancer. Eligible subjects must have had treatment with taxane, anthracycline, and at least one trastuzumab-containing regimen(s). Eligible subjects must have ErbB2 gene (or protein) amplified tumors and measurable disease as defined by RECIST or bone-only disease. The primary objective for this study is to evaluate and compare progression-free survival (PFS) in subjects with metastatic breast cancer treated with lapatinib and trastuzumab versus lapatinib monotherapy. Secondary objectives are to evaluate and compare the two treatment arms with respect to: overall survival, tumor response rate, clinical benefit, duration of response, and quality of life. Approximately 270 subjects will be enrolled into this study.

Subject: GW572016, Lapatinib, EGFR, ErbB1, HER-2/neu, ErbB2, dual kinase inhibitor, metastatic breast cancer

Author:

Revision Chronology:

UM2005/00071/00	2005-Aug-17	Original
UM2005/00071/01	2006-Jul-16	Amendment No.1: Clarifications to the study design, including the revision of some eligibility criteria, notably allowing those subjects who have had at least ONE prior trastuzumab-containing regimen (instead of two) and expansion to include Performance Status 2 subjects. The interim analysis was removed.
UM2005/00071/02	2008-MAY-27	Amendment No.02: The protocol is being amended to allow for the following changes: Update the lapatinib Core Safety Information to include data on the causal relationship of lapatinib with hepatobiliary events. Implementation of liver chemistry stopping and follow-up criteria. Minor clarifications of protocol language.
UM2005/00071/04	2009-DEC-21	Amendment No.03: Safety assessment schedule was revised from every 4 weeks to every 6 weeks. Hematology, blood chemistry and left ventricular ejection fraction, as measured by ECHO or MUGA scan, assessments were revised from every 8 weeks to every 12 weeks. Hematology and chemistry laboratory assessments will no longer be performed by a central laboratory and thus samples are no longer required to be collected and sent to the Central Laboratory Efficacy assessments were revised from every 8 weeks to a schedule

	according to local clinical practice
	Serum blood sample collection for ErbB1 and ErbB2 ELISA assay is no longer required
	FACT-B QoL questionnaire is no longer required to be completed
	Subjects discontinuing study treatment for any reason are no longer required to be followed for survival, progression or start of anti-cancer therapies.
	Subjects can receive trastuzumab at 6mg/kg every 3 weeks or at 2mg/kg every week.

Appendix 3 to Synopsis for study EGF104900

List of study sites

Worldwide study centres EGF104900

Country Name	Clinical Site Institution Name	Clinical Site Street	Clinical Site ZIP Code	Clinical Site City
Austria	LKH Salzburg	Muellner Hauptstrasse 48	A-5020	Salzburg
Austria	AKH Wien	Waehringer Guertel 18-20	A-1090	Vienna
Bulgaria	DistrDispOncDIU Plovdiv	2A, Al. Stamboliiski	4000	Plovdiv
Canada	CHUM-Hopital Notre Dame	1560 Rue Sherbrooke East, P.O. 270754	H2L 4M1	Montreal
Croatia	Klinički bolnički centar Zagreb	Klinički bolnički centar Zagreb	10 000	Zagreb
Czech Republic	Masarykuv onkologicky ustav	Zluty kopec 7	656 53	Brno
Czech Republic	FN Motol	V uvalu 84	150 08	Praha 5
Czech Republic	FN Bulovka	Na Truhlarce 100	180 00	Praha 8
Finland	Tampereen yliopistollinen sairaala	Teiskontie 35	33520	Tampere
Germany	Universitaetsfrauenklinik Magdeburg	Gerhart-Hauptmann-Str. 35	39108	Magdeburg
Germany	Vitanos GmbH	Stresemannallee 3	60596	Frankfurt
Germany	Hämato-onkologische Schwerpunktpraxis		53840	Troisdorf
Germany	MVZ Praxisklinik und Dialysezentrum		44623	Herne
Germany	Caritasklinik St. Theresia	Rheinstr. 2	66113	Saarbruecken
Germany	Onkologische Gemeinschaftspraxis		10367	Berlin
Germany	Hämato-onkologische Praxis		22767	Hamburg
Germany	Innovation Onkologie Research&Consulting GmbH	Lerchenfeld 14	22081	Hamburg
Germany	Onkologische Schwerpunktpraxis		26789	Leer
Germany	Haematologisch-onkologische Praxis		22457	Hamburg
Germany	Onkologische Praxis		42551	Velbert
Germany	Systemedic GmbH	Pruener Gang 15	24103	Kiel
Germany	Klinikum Coburg gGmbH	Ketschendorfer Str. 33	96450	Coburg
Greece	Agios Savvas Hospital	171 Alexandras Ave.	115 22	Athens
Greece	Agioi Anargiri Hospital	Xassias Avenue	13122	Athens
Greece	Metropolitan Hospital	11-13 El. Venizelou & Ethn. Macariou	18547	Neo Faliro
Italy	Ospedale R. Silvestrini	Via G. Dottori, 1	06156	Perugia
Italy	Istituto Nazionali Tumori Regina Elena	Via Elio Chianesi, 53	00144	Roma
Italy	Presidio Ospedaliero di Ravenna	Viale Randi, 5	48100	Ravenna
Italy	Istituto Clinico Humanitas	Via Manzoni, 56	20089	Rozzano (MI)
Poland	Samodzielny Publiczny Zespol Pulmonologii i Onkologii	ul. Wojska Polskiego 37	10-228	Olsztyn
Poland	Centrum Onkologii - Instytut im. Marii Sklodowskiej-Curie	ul. Roentgena 5	02-781	Warszawa
Poland	Bialostockie Centrum Onkologii	ul. Ogrodowa 12	15-027	Bialystok
Spain	Hospital General Universitario Vall d'Hebron	Passeig Vall d'Hebron 119-129	08035	Barcelona
Spain	Hospital 12 De Octubre	Ctra. De Andalucia Km 5,4	28041	Madrid
Spain	Hospital Arnau de Vilanova, Lerida	Avda Alcalde Rovira Roure 80	25198	Lerida
Spain	Hospital Duran i Reynals	Avd. Castelldefels km 2,7	08907	Hospitalet de Llobregat (Barcelona)
United Kingdom	Guy's Hospital	St. Thomas Street	SE1 9RT	London
United Kingdom	Huddersfield Royal Infirmary	Huddersfield Royal Infirmary	HD3 3EA	Huddersfield
United Kingdom	The Ipswich Hospital NHS Trust	Heath Road	IP4 5PD	Ipswich
United States	Duke University Medical Center	200 Trent Drive	27710	Durham
United States	Sammons Cancer Center	3535 Worth Street	75246	Dallas
United States	University of Pittsburgh - Magee Women's Hospital	300 Halket Street	15213	Pittsburgh
United States	Sarah Cannon Cancer Center	250 25th Avenue North	37203	Nashville
United States	Dana-Farber Cancer Institute & Harvard Medical School	44 Binney Street	02115	Boston
United States	Practice, MD		32605	Gainesville
United States	Hope Center	3702 South 4th Street	47802	Terre Haute
United States	Puget Sound Cancer Center-Seattle	1560 N 115th St, Suite G-16	98133	Seattle
United States	Practice, MD		29605	Greenville
United States	Kansas University Medical Center	340 Southwest Boulevard	66103	Kansas City
United States	Minnesota Oncology Hematology, PA	913 East 26th Street	55404	Minneapolis
United States	Memorial Healthcare Sytem Comprehensive Cancer Centers	3700 Johnson Street	33021	Hollywood
United States	Cancer Care Northwest- North	601 S Sherman Street	99202	Spokane
United States	University of Miami	1475 N.W. 12th Avenue	33136	Miami
United States	Cooper Hospital / University Medical Center	900 Centennial Boulevard	08043	Voorhees
United States	Christiana Care	4701 Ogletown Stanton Rd	19713	Newark
United States	Texas Oncology Cancer Center	6204 Balcones	78731	Austin
United States	El Paso Cancer Treatment Center	7848 Gateway East	79915	El Paso
United States	Texas Cancer Center - Denton	3720 I-35 E South	76210	Denton
United States	Yakima Valley Memorial Hospital/North Star Lodge	808 North 39th Avenue	98902	Yakima
United States	West Texas Cancer Center	301 N. Washington	79761	Odessa

United States	Northwest Medical Specialists, P.C	8915 W. Golf Road	60714	Niles
United States	Suburban Hematology-Oncology Assoicates, P.C.	6310 Professional Drive	30046-7650	Lawrenceville
United States	Carolinas Hematology- Oncology Associates	1100 S. Tyron Street	28203	Charlotte
United States	Central Indiana Cancer Centers	1346 E. County Line Road	46227	Indianapolis
United States	Florida Cancer Specialists	4331 Veronica S. Shoemaker Blvd	33916	Fort Myers
United States	Texas Oncology PA	8220 Walnut Hill Lane	75231	Dallas
United States	Palm Beach Cancer Institute	1309 North Flagler Drive	33401	West Palm Beach
United States	Florida Hospital Cancer Institute	2501 N Orange Avenue	32804	Orlando
United States	Kansas City Cancer Centers, LLC.	12200 W. 110th St.	66210	Overland Park
United States	Oncologcial practice	345 East 37th Street	10016	New York
United States	Hematology- Oncology Associates of Northern New Jersey, PA	100 Madison Avenue	07962	Morristown
United States	Southern California Permanente Medical Group	4647 Zion Ave	92120	San Diego
United States	Paris Regional Cancer Center	3550 N.E. Loop 286	75460	Paris
United States	Oncology & Hematology Associates of SW Virginia	1900 Electric Road	24153	Salem
United States	UCSF medical center	1600 Divisadero Street	94115-1710	San Francisco
United States	Texas Cancer Center at Medical City	7777 Forest Ln	75230	Dallas
United States	Missouri Cancer Associates	1705 E. Broadway	65201	Columbia
United States	Northwest Cancer Specialists- Vancouver	210 SE 136th Avenue	98684	Vancouver
United States	Mercy General Hospital	4001 J Street	95819	Sacramento
United States	Indiana University Medical Center	535 Barnhill Drive	46202	Indianapolis
United States	Aultman Hospital	2600 Sixth Street SW	44710	Canton
United States	Comprehensive Cancer Care Specialists at Boca Raton	21020 State Road 7	33428	Boca Raton
United States	Tyler Cancer Center	910 E Houston Street	75702	Tyler
United States	Allison Cancer Center	400 North Garfield	79701	Midland
United States	Overlook Oncology Center	99 Beauvoir Avenue	07901	Summit
United States	St Joseph Oncology Inc	902 North Riverside Road	64507	St. Joseph
United States	North Memorial Health Care	3435 West Broadway	55422	Robbinsdale
United States	University of Pennsylvania Hospital	3400 Spruce Street	19104	Philadelphia