CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-059

MEDICAL REVIEW(S)

Division Director Summary Review of a New Drug Application

NDA: 22-059
Drug: TYKERB® (lapatinib) Tablets
Applicant: GlaxoSmithKline
Date: March 6, 2007

Lapatinib is a 4-anilinoquinazoline kinase inhibitor of the intracellular tyrosine kinase domains of both Epidermal Growth Factor Receptor (EGFR [ErbB1]) and of Human Epidermal Receptor Type 2 (HER-2 [ErbB2]) receptors. Lapatinib inhibits ErbB-driven tumor cell growth *in vitro* and in various animal models. The applicant seeks approval of TYKERB for the following indication: "TYKERB is indicated in combination with capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 [redacted] and who have received prior therapy including an anthracycline, a taxane, and trastuzumab." A summary of the results of the randomized study supporting approval is excerpted from the revised draft labeling:

> The efficacy and safety of TYKERB in combination with capecitabine in breast cancer was evaluated in a randomized trial. Patients eligible for enrollment had HER2 (ErbB2) over-expressing, locally advanced or metastatic breast cancer, progressing after prior treatment that included taxanes, anthracyclines, and trastuzumab.
>
> Patients were randomized to receive either TYKERB 1,250 mg once daily (continuously) plus capecitabine 2,000 mg/m^2/day on days 1-14 every 21 days, or to receive capecitabine alone at a dose of 2,500 mg/m^2/day on days 1-14 every 21 days. The endpoint was time to progression (TTP). TTP was defined as time from randomization to tumor progression or death related to breast cancer. Based on the results of a pre-specified interim analysis, further enrollment was discontinued. Three hundred and ninety-nine patients were enrolled in the study. The median age was 53 years and 14% were older than 65 years. Ninety-one percent were Caucasian. Ninety-seven percent had stage IV breast cancer, 48% were ER or PR +, and 95% were ErbB2 IHC 3+ or IHC 2+ with FISH confirmation. Approximately 95% of patients had prior treatment with a taxane, an anthracycline and trastuzumab.
>
> An updated efficacy analysis four months after the interim analysis is presented in the following table:

Updated Efficacy Results

	Independent Assessment		Investigator Assessment	
	Lapatinib 1250 mg/day + Capecitabine 2000 mg/m^2/day (N=198)	**Capecitabine 2500 mg/m^2/day (N=201)**	**Lapatinib 1250 mg/day + Capecitabine 2000 mg/m^2/day (N=198)**	**Capecitabine 2500 mg/m^2/day (N=201)**
Number of Events	82	102	121	126
Median TTP, weeks	27.1	18.6	23.9	17.9
HR [95% CI]	0.57 [0.43, 0.77]		0.72 [0.56, 0.92]	
p-value	0.00013		0.00762	
RR% [95% CI]	23.7 [18.0, 30.3]	13.9 [9.5, 19.5]	31.8 [25.4, 38.8]	17.4 [12.4, 23.4]

Note: An accurate characterization of the magnitude of the PFS improvement could not be made due to missing data. No tumor assessments were available in 13% of patients after baseline for the independent assessment. The time from last tumor assessment to the data cut-off date was >100 days in 31% of patients in the independent assessment compared to 13% of patients in the investigator assessment.

At the time of the updated analysis, 30% of patients had died and the data for survival analysis are not mature. Fifty-five patients [28%] in the TYKERB plus capecitabine group and 64 subjects [32%] in the capecitabine group had died.

The safety of TYKERB has been evaluated as monotherapy or in combination with other chemotherapies for various cancers in more than 3,500 patients. The efficacy and safety of TYKERB in combination with capecitabine in breast cancer was evaluated in 198 patients in the randomized trial. Adverse events regardless of causality that occurred in at least 10% of patients in either treatment arm are shown in Table 1 below.

The most common adverse events (>25%) during therapy with TYKERB plus capecitabine were gastrointestinal (diarrhea, nausea, and vomiting) or dermatologic, such as palmar-plantar erythrodysesthesia (PPE) and rash. Diarrhea was the most common adverse event resulting in discontinuation of study medication. The most common grade 3 and 4 adverse events (NCI CTC v3) were diarrhea and PPE.

Table 1: Adverse Events (Regardless of Causality) Occurring in ≥10% of Patients

	TYKERB 1250 mg/day + Capecitabine 2000 mg/m^2/day (N = 198)			Capecitabine 2500 mg/m^2/day (N = 191)		
Event	**All Grades* %**	**Grade 3 %**	**Grade 4 %**	**All Grades* %**	**Grade 3 %**	**Grade 4 %**
Gastrointestinal disorders						
Diarrhea	65	13	1	40	10	0
Nausea	44	2	0	43	2	0
Vomiting	26	2	0	21	2	0
Stomatitis	14	0	0	11	<1	0
Abdominal pain	13	1	0	16	1	0
Dyspepsia	11	<1	0	3	0	0
Constipation	10	0	0	12	1	0
Skin and subcutaneous tissue disorders						
Palmar-plantar erythrodysaesthesia	53	12	0	51	14	0
Rash†	28	2	0	14	1	0
Dry skin	10	0	0	6	0	0
General disorders and administrative site conditions						
Fatigue	23	3	0	25	3	<1
Mucosal inflammation	15	0	0	12	2	0
Asthenia	10	1	<1	13	2	0
Metabolism and Nutrition Disorders						
Anorexia	14	<1	0	19	<1	0
Musculoskeletal and connective tissue disorders						
Pain in extremity	12	1	0	7	<1	0
Back pain	11	1	0	6	<1	0
Respiratory, thoracic, and mediastinal disorders						
Dyspnea	12	3	0	8	2	0
Nervous system disorder						
Headache	10	0	0	14	<1	<1
Psychiatric disorders						
Insomnia	10	<1	0	6	0	0

* National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

† Grade 3 dermatitis acneiform was reported in <1% of patients in TYKERB plus capecitabine group.

Selected laboratory abnormalities are shown in Table 2 below:

Table 2. Selected Laboratory Abnormalities

	TYKERB + Capecitabine			Capecitabine		
Event	**All Grades* %**	**Grade 3 %**	**Grade 4 %**	**All Grades* %**	**Grade 3 %**	**Grade 4 %**
Hematologic						
Hemoglobin	56	<1	0	53	1	0
Platelets	18	<1	0	17	<1	<1
Neutrophils	23	3	<1	31	2	1
Hepatic						
Total Bilirubin	45	4	0	30	3	0
AST	49	2	<1	43	2	0
ALT	37	2	0	3	1	0

* National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

Due to possible cardiac toxicity with HER2 (ErbB2) inhibitors (e.g., trastuzumab), LVEF was monitored in clinical trials at approximately 8-week intervals. LVEF decreases were defined as signs or symptoms of deterioration in left ventricular cardiac function that are ≥ Grade 3 (NCI CTCAE), or a ≥20% decrease in left ventricular cardiac ejection fraction relative to baseline which is below the institution's lower limit of normal. Among 198 patients who received lapatinib/capecitabine combination treatment, 3 experienced grade 2 and one had grade 3 LVEF adverse events (NCI CTC 3.0). In one patient the decrease in LVEF was not reversible. The majority (>60%) of LVEF decreases occurred within the first 9 weeks of treatment but data on long-term exposure are limited. The draft package insert advises caution if TYKERB is to be administered to patients with conditions that could impair left ventricular function and recommends that the LVEF should be evaluated in all patients prior to initiation of treatment with TYKERB to ensure that the patient has a baseline LVEF that is within the institution's normal limits and that LVEF should continue to be evaluated during treatment with TYKERB to ensure that LVEF does not decline below the institution's normal limits.

The QT prolongation potential of lapatinib was assessed as part of an uncontrolled, open-label dose escalation study in advanced cancer patients. Eighty-one patients received daily doses of lapatinib ranging from 175 mg/day to 1800 mg/day. Serial ECGs were collected on Day 1 and Day 14 to evaluate the effect of lapatinib on QT intervals. Thirteen of the 81 subjects were found to have either QTcF > 480

msec or an increase in QTcF > 60 msec. Analysis of the data suggested a relationship between lapatinib concentration and the QTc interval. The label states that lapatinib should be administered with caution to patients who have or may develop prolongation of QTc (e.g., hypokalemia, hypomagnesemia, congenital long QT syndrome, anti-arrhythmic medicines, and cumulative high-dose anthracycline therapy), that hypokalemia or hypomagnesemia should be corrected prior to lapatinib administration, and that the prescriber should consider an on-treatment electrocardiogram with QT measurement.

Other warnings and precautions include a pregnancy category D warning and a recommendation for dose reduction in patients with severe hepatic impairment. In addition, a dose reduction is recommended if TYKERB must be administered with a strong CYP3A4 inhibitor and a gradual dose increase is recommended if TYKERB must be administered with a strong CYP3A4 inducer.

Clinical Review

The Clinical Review by Qin Ryan, M.D., Ph.D., was completed on March 5, 2007. Dr. Ryan's review made the following recommendations:

1.1 Recommendation on Regulatory Action

GlaxoSmithKline has submitted a New Drug Application (NDA) #22059 for the following indication:

"Tykerb, a kinase inhibitor, is indicated in combination with capecitabine, is indicated for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 (ErbB2) and who have received prior therapy including an anthracycline, a taxane, and trastuzumab."

This reviewer recommends a regular approval for this NDA. The recommendation is based on the efficacy and safety results of a single study, EGF 100151, which is a randomized, open label trial comparing the lapatinib and capecitabine combination to capecitabine alone in patients with advanced or metastatic breast cancer. Enrollment in this study was stopped early based on IDMC recommendation after the O'Brien Fleming Boundary was crossed at a prespecified interim analysis.

The results of the primary endpoint, time to progression in interim and updated analyses were statistically significant in favor of the lapatinib-containing arm. Several sensitivity analyses supported this improvement. In addition, the response rate was statistically significant in favor of the lapatinib-containing arm. The data on overall survival analysis was immature. Although not statistically significant, there were fewer deaths on the lapatinib combination arm.

The toxicity of the lapatinib-containing arm was no worse than the capecitabine alone, except for increased incidence of diarrhea and rash. This may be because capecitabine doses were 25% higher in the control arm. There is a small incidence of decreased left ventricular function, but it is generally reversible. QT prolongation has been observed with lapatinib use but Torsade de Pointes has not been reported. The risk-benefit ratio favors the approval of this combination for the said indication.

1.2 Recommendation on Post Marketing Actions

1.2.1 Risk Management Activity

None. Please see Office of Safety review for details.

1.2.2 Required Phase 4 Commitments

1. Although study EGF 100151 terminated early and patients in the control arm have crossed over, the patients in study EGF 100151 should be followed for survival. An additional survival analysis should be performed at 75% events.

2 . Based upon the ability of lapatinib to act as a CYP 3A4 inhibitor in vitro, the Applicant agrees to perform an in vivo drug interaction study of the ability of steady-state lapatinib dosing to alter the pharmacokinetics of a single dose of midazolam. A positive finding in this study may initiate a need for further studies.

3. Based upon the ability of lapatinib to act as a CYP 2C8 inhibitor in vitro, the Applicant agrees to perform an in vivo drug interaction study of the ability of steady-state lapatinib dosing to alter the pharmacokinetics of a single dose of paclitaxel or rosiglitazone. A positive finding in this study may initiate a need for further studies.

4. Based upon the ability of lapatinib to act as a Pgp inhibitor in vitro, the Applicant agrees to perform an in vivo drug interaction study of the ability of steady-state lapatinib dosing to alter the pharmacokinetics of a single dose of digoxin. A positive finding in this study may initiate a need for further studies.

1.2.3 Other Phase 4 Requests

No additional non-clinical studies are required for lapatinib. However, the Sponsor should consider further reproductive toxicology studies to attempt to determine the nature of the toxicity that was seen in the pre- and post-natal development study in the rat. A 91% lethality rate in the offspring of rats given a dose of 120 mg/kg was seen by post neonatal day (PND) 4. A similar level of lethality was seen when another study when in utero-exposed offspring, fostered on PND 0 to non-treated dams still showed significant lethality within the first week of life. Further

investigation into a possible cause of death in the pups and into whether there is a critical time in gestation for lapatinib dosing to yield this toxicity.

Clinical Team Leader Review

The Clinical Team Leader Review concluded the following:

> Lapatinib improves TTP in a reasonably heavily pretreated patient population with advanced or metastatic breast cancer. The magnitude of improvement of TTP is not known. Although an early separation of KM curves for OS was observed, the effect of lapatinib on survival is not known. Patients on the randomized study should be followed for an effect on survival. The toxicity on the lapatinib combination arm was not much worse than on the capecitabine alone arm. However, the doses used in the capecitabine alone arm are not commonly used in clinical practice due to toxicity. Whether the capecitabine dose will need to be reduced in clinical practice when used in combination with lapatinib remains to be seen. A post-marketing commitment to study the capecitabine dose is not warranted at this time. The toxicity of the combination arm appears to be acceptable as observed in the randomized trial. The risk-benefit ratio of lapatinib in combination in the treatment population appears to be acceptable.

The review recommended the following:

> This NDA should be approved based on an improvement in time to tumor progression for the following indication:
>
> *"Tykerb is indicated in combination with capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 (ErbB2) and who have received prior therapy including an anthracycline, a taxane, and trastuzumab."*
>
> This improvement is supported by a trend towards an improvement in overall survival with early separation of the Kaplan Meier curves and an improved response rate.

Division of Medical Imaging and Hematology Products Consultation

A consultation was requested from DMIHP to evaluate the acceptability of the observed variance of TTP endpoints between assessments obtained by investigators and those of the independent reviewers in the pivotal Phase 3 Study EGF 100151 based on the data provided September 13, 2006. In a consultation dated December 18, 2006, Dr. Sheldon Kress reached the following conclusions:

> In Study EGF 100151, the primary endpoint was the independently-assessed TTP. The primary reasons for differences between the investigator and independent

reviewer assessment were due to the different interpretations in the lesion data, new lesions or the selection of different lesions by reviewers.

Utilizing the total of 121 TTP events identified by IRC at the November cut-off date, disagreement was observed in 27% of subjects. However, utilizing only those patients who were not censored disagreement was observed in 38% of subjects.

When the analysis of the major reasons for differences between investigator and independent review TTP assessments excludes the eight patients where there was agreement; however, investigator analysis of these TTP events occurred after the protocol defined number of events, the disagreement percentage becomes 32%.

Based on the data provided, the differences in percentages between the investigator assessment and independently-assessed TTP analyzed from several points of view did not exceed acceptable expectations.

Statistical Review and Evaluation

The Statistical Review and Evaluation was completed by Chia-Wen Ko, Ph.D. on March 1, 2007. The conclusions and recommendations from Dr. Ko's review are quoted below:

> In this reviewer's opinion, the study results from the submitted Phase III randomized multi-center, open-label trial indicate a statistically significant finding in efficacy based on time to disease progression or death due to breast cancer (TTP) as the primary outcome for the treatment of advanced or metastatic breast cancer in patients who have ErbB2 gene over-expression tumors and have received prior therapy including anthracyclines, taxanes, and traztuzumab. The results on all enrolled patients suggest lapatinib in combination with capecitabine had improved patient's TTP when compared to capecitabine alone (median TTP 27.1 weeks versus 17.9 weeks with hazard ratio of 0.55 per independently reviewed assessments, and 23.9 weeks versus 17.9 weeks with hazard ratio of 0.69 based on investigator determined assessments on all enrolled 399 patients). However, there is a concern that the magnitude of treatment benefit could not be accurately estimated because of a high percentage of patients with baseline only or no scans (12% by investigators and 16% by independent reviews for all enrolled patients), and because of the low percentage of complete agreement (53%) in TTP determination between investigators and independent reviews. Overall survival data at the 03April2006 analysis cut-off are not mature with 119 deaths. The updated data provide a better estimation of the median TTP over the interim data on 324 patients enrolled prior to 15Nov2005 with longer follow-up.

DSI Inspections

The Clinical Inspection Summary dated November 15, 2006 provided the following overall assessment of findings and general recommendations.

The study data collected by Dr. Franco, Dr. Kalidas, Dr. Chan, and Dr. Jagiello-Gruszfeld appear reliable. The inspection of GlaxoSmithKline and [redacted] did not identify any significant issues.

Observations noted above are based on the preliminary communications provided by the FDA field investigators. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIRs.

Clinical Pharmacology Review and Biopharmaceutics Review

The Clinical Pharmacology Review by Gene Williams, Ph.D., was completed on February 26, 2007 and made the following recommendations:

1.1. Recommendations

Assuming that our recommendations for the package insert are negotiated to satisfaction, this NDA is acceptable from the clinical pharmacology and biopharmaceutics perspective.

We request that the Sponsor submit the ECGs related to study EGF10003 to the CDER ECG warehouse.

1.2. Identify recommended Phase 4 study commitments if the NDA is judged approvable

Based upon the ability of lapatinib to act as a CYP 3A4 inhibitor in vitro, the Applicant agrees to perform an in vivo drug interaction study of the ability of steady-state lapatinib dosing to alter the pharmacokinetics of a single dose of midazolam. A positive finding in this study may initiate a need for further studies.

Based upon the ability of lapatinib to act as a CYP 2C8 inhibitor in vitro, the Applicant agrees to perform an in vivo drug interaction study of the ability of steady-state lapatinib dosing to alter the pharmacokinetics of a single dose of paclitaxel or rosiglitazone. A positive finding in this study may initiate a need for further studies.

Based upon the ability of laptinib to act as a Pgp inhibitor in vitro, the Applicant agrees to perform an in vivo drug interaction study of the ability of steady-state lapatinib dosing to alter the pharmacokinetics of a single dose of digoxin. A positive finding in this study may initiate a need for further studies.

1.3 Recommendations to the Applicant

The results of the in vitro CYP experiments (Study Report RD2000/01947/00 00AVT0021) do not include an accounting of the percentage of parent drug metabolized, nor identification (and quantitation using reference standards) of the metabolites produced. For these reasons, it is possible that unidentified CYP metabolites are being formed. The human mass balance study results, on average, failed to identify the moieity(ies) in which more than 37% of the administered 14C resides. Taken together, these data leave open the possibility that a major metabolite is formed by CYP P450s. We recommend that beginning with in vitro studies that account for the disappearance of parent and identification and quantitation of metabolites, you perform studies that will determine if major heretofore undiscovered CYP-formed metabolites occur.

The results of the in vitro CYP experiments indicate that lapatinib is a P-glycoprotein transport (Pgp) substrate. We recommend that you consider performing an in vivo drug interaction study of the effect of concomitant dosing of a strong Pgp inhibitor on the pharmacokinetics of lapatinib.

1.4 Summary of Clinical Pharmacology and Biopharmaceutics Finding

Oral absorption of lapatinib in humans is incomplete and variable. Plasma concentrations of lapatinib peak at approximately 4 hours and decline with measured half-lives of up to 14 hours. However, accumulation with daily dosing achieves steady-state in 6-7 days, suggesting an effective half-life of 24 hours.

Lapatinib is a P-glycoprotein (P-gp) substrate with an efflux ratio of 15.6 at a concentration that approximates steady-state Cmax.

The extent of absorption of lapatinib is increased 4-fold by a high-fat meal.

Lapatinib undergoes extensive metabolism to numerous oxidated and N- and O dealkylated products, with negligible urinary excretion of parent or metabolites (<2% of the dose). The most prominent metabolites identified are the carboxylic acid GSK342393 and the O-dealkylated phenol GW690006, which demonstrate pharmacological activity in vitro.

In vitro studies in human hepatocytes and hepatic microsomes indicate that lapatinib is primarily metabolized by CYP3A4 and CYP3A5 with smaller contributions from CYP2C8, and CYP2C19.

Systemic exposure to lapatinib was increased 14% in moderate and 63% in severe hepatic impairment.

Clinically relevant concentrations of lapatinib inhibit all of the CYP enzymes tested with an I/Ki ratio > 0.1. The strongest CYP inhibition was observed for

CYPs 2C8 (I/Ki = 9.2) and 3A4 (I/Ki = 5.0). Lapatinib also inhibits Pgp with an I/IC50 of 1.4.

Lapatinib exposures were reduced by 72% after CYP3A4 induction by carbamazepine, and increased to 3.6 times control after CYP3A4 inhibition by ketoconazole.

Mixed-effects modeling of the Fridericia corrected QT interval (QTcF) indicated a significant relationship between lapatinib concentration and the QTcF interval. Based on the model parameters, the predicted change in QTcF was estimated at peak concentrations following the recommended dose of lapatinib (1250 mg/day in combination with capecitabine)... At the mean peak concentration (Cmax) of 3203 ng/ml following the 1250 mg daily dose, the predicted change in QTcF was estimated to be 13.5 msec... Using the upper 95% confidence limit of the slope estimate, the predicted QTcF prolongation at the mean Cmax was estimated to be 23.4 msec. Additionally, factors that could increase lapatinib concentrations, such as co-administration of CYP3A4 inhibitors, administration of drug with food, or administration to patients with hepatic impairment, would be expected to further prolong the QTc interval.

Interdisciplinary Review Team for QT Studies Consultation

The IRT consultation of December 14, 2006 made the following recommendations which were incorporated into the draft labeling:

The total evidence of the data indicates that lapatinib prolongs the QTc interval. Therefore, the IRT recommends that the product label be revised to include the following information.

Under Clinical Pharmacology:

The QT prolongation potential of lapatinib was assessed as part of an uncontrolled, open-label dose escalation study of lapatinib in advanced cancer patients. Eighty-one (81) patients received daily doses of lapatinib ranging from 175 mg/day to 1800 mg/day. Serial ECGs were collected on day 1 and day 14 to evaluate the effect of lapatinib on QT intervals. Thirteen of the 81 subjects were found to have either QTcF (corrected QT by the Friedericia method) > 480 msec or an increase in QTcF > 60 msec. Analysis of the data suggested a relationship between lapatinib concentration and the QTc interval.

Under Precautions or Warnings:

Lapatinib should be administered with caution to patients who have or may develop prolongation of QTc. These conditions include patients with hypokalemia or hypomagnesemia, with congenital long QT syndrome,

patients taking anti-arrhythmic medicines or other medicinal products that lead to QT prolongation, and cumulative high-dose anthracycline therapy. Hypokalemia or hypomagnesemia should be corrected prior to lapatinib administration.

Please ask the Sponsor to submit ECGs related to study EGF10003 to the ECG warehouse.

Pharmacology/Toxicology Review and Evaluation

The Pharmacology/Toxicology Review and Evaluation by Kimberly Benson, Ph.D., was completed on March 5, 2007 and made the following recommendations:

A. Recommendation on approvability
Approvable. The non-clinical studies with oral lapatinib support the safety of its use in metastatic breast cancer.

B. Recommendation for nonclinical studies
No additional non-clinical studies are required for lapatinib. However the Sponsor should consider further reproductive toxicology studies to attempt to determine the nature of the toxicity that was seen in the pre- and post-natal development study in the rat. A 91% lethality rate in the offspring of rats given a dose of 120 mg/kg was seen by Post Natal Day (PND) 4. A similar level of lethality was seen when another study when in utero-exposed offspring, fostered on PND 0 to non-treated dams still showed significant lethality within the first week of life. Further investigation into a possible cause of death in the pups and into whether there is a critical time in gestation for lapatinib dosing to yield this toxicity.

Should QT prolongation adverse events become more prevalent when Tykerb use increases once the drug is approved, the sponsor may consider conducting a hERG assay. This could identify and IC50 for the inhibition of the hERG channel.

C. Recommendations on labeling
The recommendations to the sponsor's proposed labeling are given, with a detailed report regarding the rationale for the recommended changes, in a subsequent review.

Supervisory Pharmacologist Memorandum

The Supervisory Pharmacologist Memorandum of March 5, 2007 by John Leighton, Ph.D. concurred "with Dr. Benson's conclusion that pharmacology and toxicology data support the approval of NDA 22-059, TYKERB. There are no outstanding nonclinical issues related to the approval of TYKERB."

Chemistry Review

The Chemistry Review dated December 18, 2006 made the following recommendations:

A. Recommendation and Conclusion on Approvability

> The application is recommended for approval with respect to the chemistry, manufacturing, and controls (CMC).
>
> However, this recommendation assumes that the pharmacology/toxicology team finds the applicants drug substance and drug product impurities acceptance criteria to be acceptable from a safety perspective (pending review for 22-SEP-2006, consult request). An unacceptable recommendation from the pharmacology/toxicology team may have implications with regard to the drug substance and drug product impurities acceptance criteria and/or the retest and expiration dating periods, respectively.
>
> Although the applicant has not responded to Comments 5-7 of the 06-DEC-2006, IR letter, the comments are not considered approvability issues as they do not affect the overall quality assurance of the product. These comments are intended to gain further product knowledge and process understanding from the applicant under the ONDQA pilot program. They can be addressed post-approval due to the short review timeline.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The following comments and risk management statements regarding CMC should be included in the action letter:

1. As indicated in our teleconference on November 16, 2006, your proposed CMC Regulatory Agreement submitted as part of the CMC Pilot Program is under review. Your proposal outlines the regulatory mechanisms for managing changes related to process design and control spaces post-approval. While a mutually accepted CMC Agreement is not a condition for the approval of this application, it will have implications for post-approval changes. Therefore, you are reminded that, until the CMC Agreement is approved, the existing regulations and guidances should be followed, as appropriate for the post approval CMC changes.

2. We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

ONDQA Deputy Director's CMC Memorandum

The December 18, 2006 memorandum by Dr. Chi-wan Chen made the following recommendation:

> The application is recommended for approval from the CMC standpoint. Although the applicant has not responded to certain QbD-related comments in the 06-DEC-2006 IR letter, they are not considered approvability issues as they do not affect the overall quality assurance of the product. These comments are intended to gain further product knowledge and process understanding from the applicant under the ONDQA pilot program. They can be addressed post-approval due to the short review timeline.

DMETS Consultation

The DMETS consultation of November 17, 2006 made the following recommendations:

1. DMETS has no objections to the use of the proprietary name Tykerb from a safety perspective. This is considered a final decision. However, if the approval of this NDA is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review in order to minimize potential errors with the use of this product.

3. We recommend consulting Guirag Poochikian, Chair of the CDER Labeling and Nomenclature Committee for the proper designation of the established name.

4. DDMAC finds the proprietary names Tykerb acceptable from a promotional perspective...

III. In the review of the container labels, carton and insert labeling of Tykerb, DMETS has focused on safety issues relating to possible medication errors. DMETS has identified the following areas of improvement, which might minimize potential user error.

1 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

The DMETS comments regarding container and carton labels have been communicated to the sponsor and revised labels have been submitted. The labeling comments have been incorporated as indicated during the labeling meetings.

SEALD Comments on Draft Labeling

A consultation by Iris Masucci, PharmD, of the Study Endpoints and Label Development Team was completed on December 19, 2006. The recommendations in the consultation were considered and incorporated as indicated during the labeling meetings.

DSRCS Consultation

The DSCRCS consultation on the patient information is pending.

DDMAC Consultation

A DDMAC consultation by Joseph Grillo was completed on October 20, 2006. The comments were considered and incorporated as indicated during the labeling meetings.

Conclusions and Recommendations

I concur with the reviewers' recommendations for approval of this NDA. Although I am concerned that there is a discrepancy between the independent and investigator assessments of the primary endpoint of time to progression (TTP), both assessments result in clinically and statistically significant improvements in TTP. The median TTP by independent assessment was 27.1 weeks for the combination vs. 18.6 weeks for capecitabine alone (HR 0.57, p=0.00013). The median TTP by investigator assessment was 23.9 weeks for the combination vs. 18.3 weeks for capecitabine alone (HR=0.72, p=0.00762). The survival data are not yet mature. While the improvement in TTP with the addition of lapatinib is modest, it is attained with a minimal increase in toxicity over that seen with capecitabine alone and in a population that has received multiple prior therapies. I also concur with the recommended phase 4 commitments. Once the DSRCS consult on the patient information has been completed and final agreement has been reached on the label and the postmarketing commitments, the application should be approved.

Robert L. Justice, M.D., M.S.
Division Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Office of New Drugs
Center for Drug Evaluation and Research

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MEDICAL OFFICER

CLINICAL TEAM LEADER'S REVIEW OF AN NDA
DIVISION OF DRUGS ONCOLOGY PRODUCTS
OFFICE OF ONCOLOGY

NDA	22,059
Drug Name	Lapatinib
Trade Name	Tykerb
Submission Code	000
Priority Designation:	Priority review
Applicant	GlaxoSmithKline
Indication	TYKERB in combination with capecitabine, is indicated for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 (ErbB2) and who have received prior therapy including an anthracycline, a taxane, and trastuzumab.
Letter Date	August 25th, 2006

Recommendation:
This NDA should be approved based on an improvement in time to tumor progression for the following indication:

"Tykerb is indicated in combination with capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 (ErbB2) and who have received prior therapy including an anthracycline, a taxane, and trastuzumab."

This improvement is supported by a trend towards an improvement in overall survival with early separation of the Kaplan Meier curves and an improved response rate.

Introduction:
Lapatinib is an orally formulated tyrosine kinase inhibitor, of ErbB1 and ErbB2. The significance of te dual inhibition is not known. An ErbB2 inhibitor, trastuzumab is approved.

Study Design:
EGF 1000151 was the major, prospectively randomized; international trial that supported the efficacy and safety in this NDA submission. Patients with advanced or metastatic breast cancer whose tumors overexpress HER2 (ErbB2) and who have received prior therapy including an anthracycline, a taxane, and trastuzumab were enrolled. The study was conducted in North America, Europe, South Africa, Hong Kong, Israel and Australia.

The two treatment arms were as follows:

Table 1: Treatment Arms with Regimens Administered

Treatment Arm	Dose	Times Per Day	Days of Administration	Cycle
capecitabine	capecitabine 2500 mg/m2/day	Divided in twice daily dosage	d1-14	q 21 days
lapatinib + capecitabine	lapatinib 1250 mg/day	Once daily	q day continuously	q 21 days

	capecitabine 2000 mg/m2/day	Divided in twice daily dosage	d1-14	

According to the protocol, the study was to enroll 528 patients. Two interim analyses were planned. After 146 investigator-identified events in 321 patients, the first interim analysis was conducted. The Independent Data Monitoring Committee (IDMC) suggested discontinuing further enrollment because the prespecified O'Brien-Fleming Boundary set at 0.0038 was crossed with a p value of 0.00008 based on analysis on TTP. When the boundary was adjusted for the 121 Independent review identified events, the results were similar at p of $\leq$0.0014. Three hundred and ninety-nine patients were enrolled before further enrollment was discontinued, and patients were allowed to cross over to the lapatinib combination arm. On FDA's request, the efficacy and safety results were submitted by the applicant for the April 3rd cut-off date (submitted on 10/4/2006). Per protocol, the blinded independent review was to be the basis of the primary analysis. The investigator assessments were the basis for treatment decisions including discontinuation of treatment.

Efficacy Results:
Overall, the submitted randomized trial was well-designed and well-conducted. The median age of all patients was 53 years. The majority were white (91%), and all patients enrolled in this study were female. Overall, 77% of the patients were post-menopausal (lapatinib + capecitabine: 81%; capecitabine: 72%). Forty-nine percent patients were ER/PR (-). Approximately 45% patients had received prior hormonal therapy. Forty-four percent had received prior vinorelbine and 12% had received gemcitabine.

TTP:
TTP was defined as time from randomization to disease progression or death due to breast cancer. Scans or photographs provided evidence of tumor progression that was assessed by the blinded, independent review committee (IRC). Most of the progressions were based on tumor progressions observed on CT scans and drove the results of the study. The results of the TTP analyses are summarized in table 2. The lapatinib combination arm was consistently statistically superior to the capecitabine alone arm whether at the interim analysis or at the updated analysis. However, the magnitude of TTP according to the IRC at the Nov 15 cut off date with a median of 17.6 weeks was very different from the IRC assessment at the April 3rd cutoff. It was also different from the investigators (INV) analyses at the November and April cut off dates. The median TTP ranged form 5.6 to 8 weeks in the IRC analysis at the update and the INV analyses at both time points.

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TTP	NOV 15 2005 CUT-OFF N = 324				APR 3 2006 CUT-OFF N = 399			
	IRC		INV		IRC		INV	
	LC	C	LC	C	LC	C	LC	C
Total Events (%)	49 (30%)	72 (45%)	59 (36%)	74 (46%)	82 (41%)	102 (51%)	121 (61%)	126 (63%)
Median TTP, weeks	36.7	19.1	25.9	18.9	27.1	18.6	23.9	18.3
Improvement in median TTP, weeks	17.6		7		8.5		5.6	
HR [95% CI]	0.48 [0.33, 0.70]		0.59 [0.42, 0.84]		0.55 [0.41, 0.74]		0.72 [0.56, 0.92]	
p-value	0.00008		0.00219		0.00013		0.00762	

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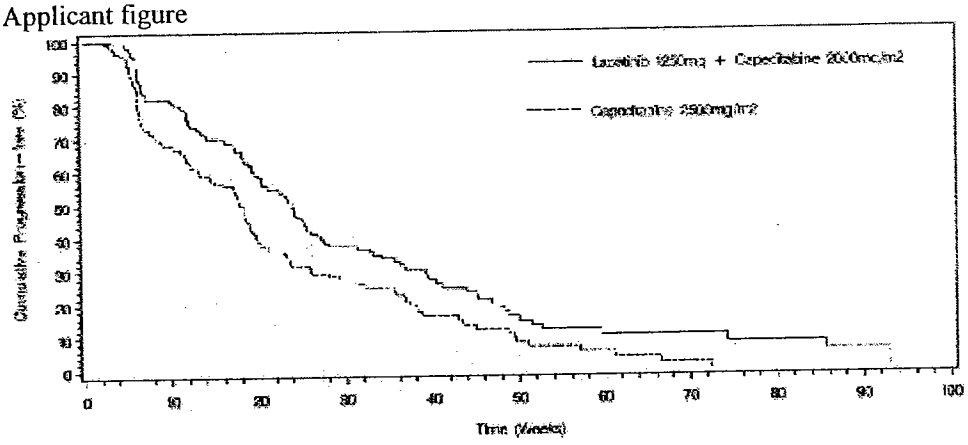
Figure 1: Kaplan Meier Estimates of TTP- Independent Review Analysis (April 3rd Cut off date)

Applicant figure



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4- According to FDA clinical reviewer, Dr Qin Ryan MD, PhD, no tumor assessments were available in 13% of patients at all or after baseline for independent assessment. The time from last tumor assessment to the data cut-off date was greater than100 days in 31% of patients in the independent assessment compared to 13% of patients in the investigator assessment. The presence of this missing data prevents accurate characterization of the magnitude of improvement in TTP.

Multiple sensitivity analyses were performed to assess the TTP improvement and its magnitude. All of these analyses except for one extreme analysis were in favor of the lapatinib combination arm. This analysis was termed the worst case scenario. In this analysis, where a discrepancy existed between the IRC and INV, the earlier of the two dates from INV or IRC assessment was chosen for the lapatinib arm and the later of the dates was chosen for the capecitabine alone arm. The statistical advantage for lapatinib disappeared in this analysis. Please see the table below for a summary and refer to the statistical review by Dr Ko PhD for details.

Table 3: Summary of Sensitivity Analysis conducted by The FDA Statistical Reviewer on TTP

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Per-Protocol analysis (by limiting the TTP analyses to patients without major protocol violations):	9.5	<0.00001
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TTP analyses based on revised data (by replacing IRC TTP with INV TTP whenever IRC TTP > INV TTP; and replacing IRC TTP with INV TTP when IRC TTP censored, but INV TTP event observed at later date):	14.3	0.00017
Impact of the 75 enrolled patients (by evaluating results with the 324 early enrolled patients only):	11.3	0.00013
TTP analysis excluding deaths due to breast cancer as events	12.7	0.00025
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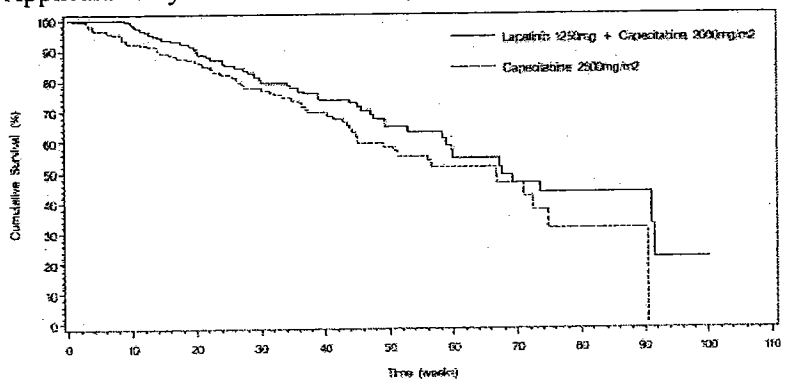
Overall Survival:

At the time of the updated analysis, 30% of patients had died and the data for survival analysis were not mature. Fifty-five patients (28%) in the lapatinib combination group and 64 patients (32%) in the capecitabine group had died. Hazard Ratio for overall survival was 0.78; 95%CI: 0.55-1.12. The p value unadjusted for multiplicity was 0.177.

Figure: Kaplan Meier Curve for OS at the Updated Analysis

Applicant analysis



Response Rate:
Response rate was higher on the lapatinib combination arm with minimal overlap in the 95% CI only in the IRC review assessment.

Table: Response Rate and Duration of Response at the Updated Analysis

	NOV 15 2005 CUT-OFF N = 399			
	IRC		INV	
	LC	C	LC	C
Response Rate	23.7	13.9	31.8	17.4
95% Confidence Interval	[18.0, 30.3]	[9.5, 19.5]	[25.4, 38.8]	[12.4, 23.4]

LC: lapatinib + capecitabine
C: capecitabine
IRC: Independent review
INV: Investigator review

The duration of response was assessed by the FDA statistical reviewer and was similar in both arms at the Nov 15th, 2006 interim analysis. It was defined as the time from first documented evidence of PR or CR until the first documented sign of disease progression or death due to breast cancer in responding patients. Based on data from the updated analysis, the median duration of response was 32.1 weeks in the lapatinib combination arm and 30.6 weeks in the capecitabine group.

Safety:
One hundred and ninety eight patients received lapatinib in combination with capecitabine in this randomized study. The dose of capecitabine was different in the two arms. The control arm had the higher dose of 2500 mg/m^2/d compared to 2000 mg/m^2/day when used in combination with lapatinib. It is noted that although approved at the higher dose, capecitabine is usually administered at a lower dose in clinical practice due to toxicity.

The duration of exposure to study drugs was slightly longer on the lapatinib arm (19.3 vs. 18.9 weeks). Approximately 90% patients experienced at least one adverse event. The incidence of Serious Adverse Events (SAE) was similar on both arms (24%). Thirteen percent patients on the lapatinib arm and 11% on the capecitabine alone arm discontinued treatment due to AEs. Diarrhea was the most common adverse event resulting in discontinuation of study medication. Fatal SAE were similar on the two arms (lapatinib combination arm: 1%; capecitabine arm: 2%). The most common adverse events (>25%) during therapy with lapatinib + capecitabine were gastrointestinal (diarrhea, nausea, and vomiting) or dermatologic, such as palmar-plantar erythrodysesthesia (PPE) and rash. The incidence of grade 3/4 events of these AEs was similar on the two arms, although the overall incidence of diarrhea and rash was greater on the lapatinib combination arm. Patients were monitored on study for decreases in LVEF. Out of the 7 patients identified with LVEF decrease on the lapatinib combination arm, 2 patients had a grade 2 event and 1 patient had a grade 3 event. LVEF decrease was not reversible in 1 patient. QT prolongation was identified in a single arm study, and patients should be monitored for this so as to optimize electrolytes to prevent torsade de pointes. No case of torsade de pointes has been reported so far.

Other Considerations:
CYP3A4 inhibitors may increase and CYP3A4 inducers may decrease the AUC of lapatinib. Patients on these drugs were excluded from the randomized study. The doses of lapatinib on these drugs should be studied further. Lapatinib is a substrate of the efflux transporter P-

glycoprotein. Caution should be exercised when administering it it with drugs that inhibit Pgp, such as digoxin. These factors have been taken into consideration for the post marketing commitments. In addition, the AUC of lapatinib increases if taken in divided doses. It is important that patients be advised not to divide the lapatinib doses. This warning will be included in the label and in the patient information leaflet.

Lapatinib should not be administered to pregnant females. The effect of lapatinib on human fertility is unknown. However, when female rats were given oral doses of lapatinib during breeding and through the first 6 days of gestation, a significant decrease in the number of live fetuses was seen at 120 mg/kg/day and in the fetal body weights at $\geq$ 60 mg/kg/day (approximately 6.4 times and 3.3 times the expected human clinical exposure based on AUC, respectively).

Conclusion:
Lapatinib improves TTP in a reasonably heavily pretreated patient population with advanced or metastatic breast cancer. The magnitude of improvement of TTP is not known. Although an early separation of KM curves for OS was observed, the effect of lapatinib on survival is not known. Patients on the randomized study should be followed for an effect on survival. The toxicity on the lapatinib combination arm was not much worse than on the capecitabine alone arm. However, the doses used in the capecitabine alone arm are not commonly used in clinical practice due to toxicity. Whether the capecitabine dose will need to be reduced in clinical practice when used in combination with lapatinib remains to be seen. A post-marketing commitment to study the capecitabine dose is not warranted at this time. The toxicity of the combination arm appears to be acceptable as observed in the randomized trial. The risk-benefit ratio of lapatinib in combination in the treatment population appears to be acceptable.

Amna Ibrahim MD
Acting Clinical Team Leader

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/s/

Amna Ibrahim
3/6/2007 09:53:30 AM
MEDICAL OFFICER

CLINICAL TEAM LEADER'S REVIEW OF AN NDA
DIVISION OF DRUGS ONCOLOGY PRODUCTS
OFFICE OF ONCOLOGY

NDA	22,059
Drug Name	Lapatinib
Trade Name	Tykerb
Submission Code	000
Priority Designation:	Priority review
Applicant	GlaxoSmithKline
Indication	TYKERB in combination with capecitabine, is indicated for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 (ErbB2) and who have received prior therapy including an anthracycline, a taxane, and trastuzumab.
Letter Date	August 25th, 2006
Original Review:	March 6th, 2007
Amended Review:	March 12th, 2007

Recommendation:
This NDA should be approved based on an improvement in time to tumor progression for the following indication:

"Tykerb is indicated in combination with capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 (ErbB2) and who have received prior therapy including an anthracycline, a taxane, and trastuzumab."

This improvement is supported by a trend towards an improvement in overall survival with early separation of the Kaplan Meier curves and an improved response rate.

Introduction:
Lapatinib is an orally formulated tyrosine kinase inhibitor, of ErbB1 and ErbB2. The clinical significance of the dual inhibition is not known. An ErbB2 inhibitor, trastuzumab (Herceptin) is approved for treatment of Breast cancer patients for adjuvant use as part of a treatment regimen, and as a single agent and as part of combination treatment of patients with breast cancers whose tumors overexpress ErbB2 (HER2).

Study Design:
EGF 1000151 was the major, prospectively randomized, international trial that supported the efficacy and safety in this NDA submission. Patients with advanced or metastatic breast cancer whose tumors overexpress HER2 (ErbB2) and who have received prior therapy including an anthracycline, a taxane, and trastuzumab were enrolled. The study was conducted in North America, Europe, South Africa, Hong Kong, Israel and Australia.

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According to the protocol, the study was to enroll 528 patients. Two interim analyses were planned. After 146 investigator-identified events in 321 patients, the first interim analysis was conducted. The Independent Data Monitoring Committee (IDMC) suggested discontinuing further enrollment because the prespecified O'Brien-Fleming Boundary set at 0.0038 was crossed with a p value of 0.00008 based on analysis on TTP. When the boundary was adjusted for the 121 Independent review identified events, the results were similar at p of $\leq$0.0014. Three hundred and ninety-nine patients were enrolled before further enrollment was discontinued, and patients were allowed to cross over to the lapatinib combination arm. On FDA's request, the efficacy and safety results were submitted by the applicant for the April 3rd cut-off date (submitted on 10/4/2006). Per protocol, the blinded independent review was to be the basis of the primary analysis. The investigator assessments were the basis for treatment decisions including discontinuation of treatment.

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HR [95% CI]	0.48 [0.33, 0.70]		0.59 [0.42, 0.84]		0.57 [0.43, 0.77]		0.72 [0.56, 0.92]	
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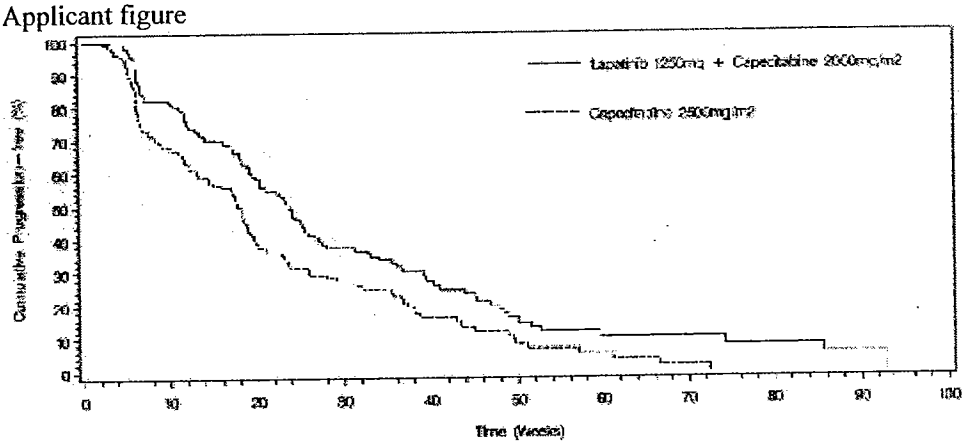

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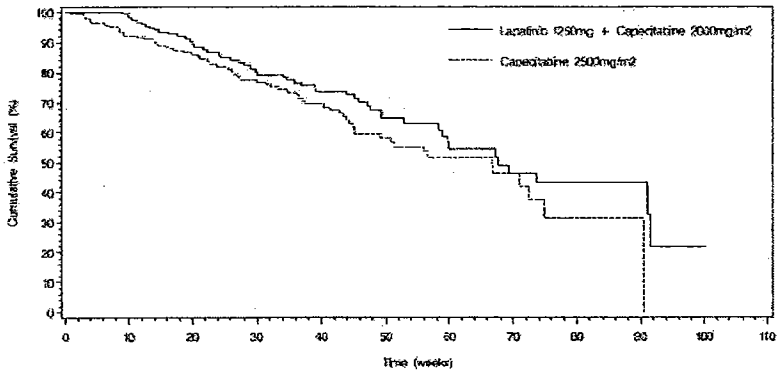
Applicant analysis



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Amna Ibrahim MD
Acting Clinical Team Leader

Note: *This is an amended Team Leader review.*

1- *It incorporates changes that have been made to the Hazard Ratio and the 95% CI for TTP for the April 3rd cut-off analysis. These changes reflect the efficacy results presented in the label. These values are now based on the applicant's method of statistical analysis and are slightly different from the FDA statistical team's analysis using the Kaplan*

Meier method. In the Applicant's method, an event is counted only once, i.e. either at progression or at death. The applicant's method is acceptable.

2- *The phrase "based on machine readings" has been added to the last paragraph in the safety section to reflect the input from GSK during labeling, and confirmed by the clinical pharmacology reviewer, Dr Ramchandani.*

3- *This amended review also has an expanded introduction to include the approved indications for trastuzumab (Herceptin), a related drug. These were inadvertently deleted from the original review. The font on the introductory paragraph has been "unbolded".*

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/s/

Amna Ibrahim
3/12/2007 11:23:31 AM
MEDICAL OFFICER
Amended Team Leader's review

CLINICAL REVIEW

Application Type	NDA
Submission Number	22059
Submission Code	000
Letter Date	September 13, 2006
Stamp Date	September 13, 2006
PDUFA Goal Date	March 13, 2007
Reviewer Name	Qin Ryan
Review Completion Date	March 5, 2007
Review Amendment date	March 12, 2007
Established Name	Lapatinib
(Proposed) Trade Name	Tykerb
Therapeutic Class	TKI
Applicant	GlaxoSmithKline
Priority Designation	P
Formulation	Oral
Dosing Regimen	1250 mg QD
Indication	Metastatic breast cancer
Intended Population	Previously treated

Amendment Summary

After the completion of this NDA review, the applicant submitted additional information regarding resolution of an adverse event of left ventricular systolic dysfunction, which was the only irreversible case that reported in the safety update. This amendment is to include this reviewer's assessment on this new information. In addition, some administrative amendment was also made to correct some typographical errors.

Table of Contents

TABLES

FIGURES

EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

GlaxoSmithKline has submitted a New Drug Application (NDA) #22059 for the following indication:

"Tykerb is indicated in combination with capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 (ErbB2) and who have received prior therapy including an anthracycline, a taxane, and trastuzumab."

This reviewer recommends a regular approval for this NDA. The recommendation is based on the efficacy and safety results of a single study, EGF 100151, which is a randomized, open label trial comparing the lapatinib and capecitabine combination to capecitabine alone in patients with advanced or metastatic breast cancer. Enrollment in this study was stopped early based on IDMC recommendation after the O'Brien Fleming Boundary was crossed at a prespecified interim analysis.

The result of the primary endpoint, time to progression in interim and updated analyses were statistically significant in favor of the lapatinib-containing arm. Several sensitivity analyses supported this improvement. In addition, the response rate was statistically significant in favor of the lapatinib-containing arm. The data on overall survival analysis was immature. Although not statistically significant, there were fewer deaths on the lapatinib combination arm.

The toxicity of the lapatinib-containing arm was no worse than the capecitabine alone, except for increased incidence of diarrhea and rash. This may be because capecitabine doses were 25% higher in the control arm. There is a small incidence of decreased left ventricular function, but it is generally reversible. QT prolongation has been observed with lapatinib use but Torsade de Pointes has not been reported. The risk-benefit ratio favors the approval of this combination for the said indication.

1.2 Recommendation on Post Marketing Actions

1.2.1 Risk Management Activity

None. Please see Office of Safety review for details.

1.2.2 Required Phase 4 Commitments

1. Although study EGF 100151 terminated early and patients in the control arm have crossed over, the patients in study EGF 100151 should be followed for survival. An additional survival analysis should be performed at 75% events.

2 . Based upon the ability of lapatinib to act as a CYP 3A4 inhibitor in vitro, the Applicant agrees to perform an in vivo drug interaction study of the ability of steady-state lapatinib dosing to alter the pharmacokinetics of a single dose of midazolam. A positive finding in this study may initiate a need for further studies.

3. Based upon the ability of lapatinib to act as a CYP 2C8 inhibitor in vitro, the Applicant agrees to perform an in vivo drug interaction study of the ability of steady-state lapatinib dosing to alter the pharmacokinetics of a single dose of paclitaxel or rosiglitazone. A positive finding in this study may initiate a need for further studies.

4. Based upon the ability of lapatinib to act as a Pgp inhibitor in vitro, the Applicant agrees to perform an in vivo drug interaction study of the ability of steady-state lapatinib dosing to alter the pharmacokinetics of a single dose of digoxin. A positive finding in this study may initiate a need for further studies.

1.2.3 Other Phase 4 Requests

No additional non-clinical studies are required for lapatinib. However, the Sponsor should consider further reproductive toxicology studies to attempt to determine the nature of the toxicity that was seen in the pre- and post-natal development study in the rat. A 91% lethality rate in the offspring of rats given a dose of 120 mg/kg was seen by post neonatal day (PND) 4. A similar level of lethality was seen when another study when in utero-exposed offspring, fostered on PND 0 to non-treated dams still showed significant lethality within the first week of life. Further investigation into a possible cause of death in the pups and into whether there is a critical time in gestation for lapatinib dosing to yield this toxicity.

1.3 Summary of Clinical Findings

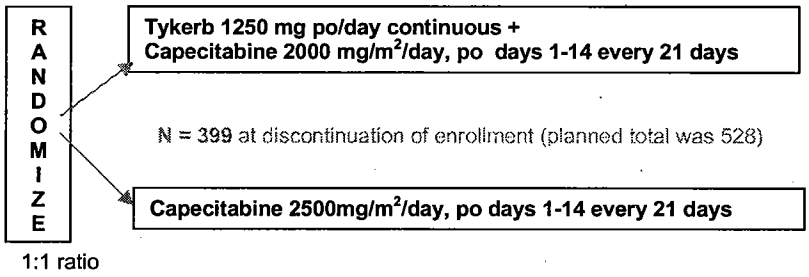
A single randomized study EGF 100151 in patients with locally advanced or metastatic breast cancer whose tumors overexpress HER2 (ErbB2) and who have received prior therapy including an anthracycline, a taxane, and trastuzumab, lapatinib in combination with capecitabine treatment supports the efficacy and safety of lapatinib in this NDA. It has demonstrated superiority in time to tumor progression and response rates compared to capecitabine alone. The magnitude of the lapatinib efficacy cannot be precisely measured in this study due to missing tumor assessments. A trend towards improved overall survival (OS) was observed. The safety profile of lapatinib in combination with capecitabine is acceptable in the study population.

1.3.1 Brief Overview of Clinical Program

Lapatinib (Tykerb) is an orally formulated tyrosine kinase inhibitor of both ErbB1 and ErbB2. The efficacy and safety of lapatinib in combination with capecitabine in breast cancer was evaluated in a randomized trial. Patients eligible for enrollment had HER2 (ErbB2) over-expressing, locally advanced or metastatic breast cancer, progressing after prior treatment that included taxanes, anthracyclines, and trastuzumab. HER2 (ErbB2) over-expression had been confirmed by IHC 3+ or

IHC 2+ with FISH confirmation prior to entering the study. The primary objective of the study was to evaluate and compare time to progression (TTP) in subjects with refractory advanced or metastatic breast cancer treated with lapatinib and capecitabine versus capecitabine alone. Based on the results of a pre-specified interim analysis, further enrollment was discontinued. Three hundred and ninety-nine patients were enrolled in this study.

Figure 1: Treatment arms in study EGF 100151



Subjects were randomized to one of two treatment arms, as shown in the figure above. Treatment was administered until disease progression or withdrawal from study due to unacceptable toxicity or other reasons. Treatment could have been delayed up to 2 weeks or a single reduction in the lapatinib dose was allowed to 1000 mg/day to allow for resolution of toxicity. A delay for up to 2 weeks and dose reductions to 50% of the starting dose were also permitted for capecitabine.

Efficacy assessments were performed every 6 weeks for the first 24 weeks, then every 12 weeks and at the end of treatment. Subjects withdrawn from investigational drug who had not progressed were assessed every 12 weeks until progression. Thereafter, subjects were followed for survival at approximately 12-week intervals until death. All tumor response assessments underwent a blinded independent review of objective evidence (e.g., radiological scans and medical photographs).

An interim analysis was planned after 133 events (30% of disease progression or death due to breast cancer prior to progression) had been reported. At the clinical cut-off date (Nov 15 2005), 146 investigator-identified events were reported in 324 subjects. All available imaging studies and photographic assessments obtained on these subjects were assessed for response and progression based on RECIST criteria by a blinded independent review committee (IRC). The IRC determined that 121 subjects had met the criteria for a protocol-defined TTP event. The interim analysis was conducted by an external contract research organization in order to maintain the blind of the study sponsor. Following their review of the interim analysis, the Independent Data Monitoring Committee (IDMC) unanimously recommended termination of study enrollment as the protocol-defined superiority boundary for the lapatinib + capecitabine group was exceeded. The applicant stopped further enrollment on Apr 3 2006, and the protocol was amended from May 12 2006 (amendment 7) so that subjects in the capecitabine monotherapy group were allowed to crossover to receive lapatinib + capecitabine. FDA requested an updated analysis for efficacy for TTP and overall survival (OS) in addition to the safety update at the time when further enrollment was discontinue on April 3, 2006.

1.3.2 Efficacy

Three hundred and twenty four patients were enrolled in the study by the interim analysis. By the time of the discontinuation of further enrollment on April 3, 2006, 399 patients were enrolled, 76% of the 528 patients planned. The median age was 53 years and 14% were older than 65 years. Ninety-one percent were Caucasian. Ninety-seven percent had stage IV breast cancer, 48% were ER or PR +, and 95% were ErbB2 IHC 3+ or IHC 2+ with FISH confirmation. Approximately 95% of patients had prior treatment with a taxane, an anthracycline and trastuzumab. The more mature data from the updated efficacy analyses were chosen for the label after discussion within this division (DDOP) and the Office of Oncology, and within the biostatistics division and office. Due to missing tumor assessments, the magnitude of the TTP improvement of lapatinib cannot be precisely characterized. Thirteen percent patients had either no tumor assessments (10%) available for the independent review, or were without adequate tumor assessments (3%) as evaluated by the independent review. The time from last tumor assessment to the data cut-off date was greater than 100 days in 31% of patients in the independent assessment compared to 13% of patients in the investigator assessment.

Table 1: Efficacy of lapatinib in combination with capecitabine (ITT, Apr 3 2006 cut-off)

	Independent Assessment		**Investigator Assessment**	
	Lapatinib + Capecitabine (N=198)	**Capecitabine (N=201)**	**Lapatinib + Capecitabine (N=198)**	**Capecitabine (N=201)**
Total Events	82	102	121	126
Median TTP, weeks	27.1	18.6	23.9	18.3
HR [95% CI]	0.57 [043, 0.77]		0.72 [0.56, 0.92]	
p-value	0.00013		0.00762	
RR% [95% CI]	23.7 [18.0, 30.3]	13.9 [9.5, 19.5]	31.8 [25.4, 38.8]	17.4 [12.4, 23.4]

1.3.3 Safety

Safety of lapatinib has been evaluated as monotherapy or in combination with other chemotherapies for various cancers in more than 3,500 patients, including 198 patients who received lapatinib in combination with capecitabine in study EGF100151. The safety analyses indicated that oral lapatinib 1250 mg once daily taken continuously in combination with 2000 mg/m^2/day capecitabine for 14/21 days has an acceptable risk-benefit ratio in patients with advanced/metastatic breast cancer. The mean treatment duration of lapatinib combination arm at the time of clinical update (Apr 3 2006) was 6 weeks longer than that of capecitabine alone arm (21 weeks versus 15 weeks), because of the overall longer time to disease progression on the lapatinib combination arm. Even though the mean daily exposure of capecitabine is 400 mg/m^2 lower for the lapatinib combination arm (2000 mg/m^2 versus 2400 mg/m^2), the mean cumulative dose of capecitabine was 16 g/m^2 higher for the lapatinib arm (170 g/m^2 versus 154 g/m^2).

The most common adverse events (>15%) during therapy with lapatinib plus capecitabine were gastrointestinal (60% diarrhea, 44% nausea, and 26% vomiting) or dermatologic, such as palmar-plantar erythrodysesthesia (PPE, 53%), rash (28%), fatigue (23%), and stomatitis (14%). The most common grade 3 or 4 events were diarrhea (14%) and PPE (12%) for the lapatinib and capecitabine combination. Thirteen percent patients discontinued therapy due to any AE and 5% discontinued due to diarrhea in the lapatinib + capecitabine arm. The important laboratory AEs were anemia (60%), neutropenia (24%), thrombocytopenia (19%) and abnormalities of transaminases (60%) and bilirubin (43%), similar to those observed on the control arm.

There was no death on lapatinib combination arm during the first 60 days of study. Four percent patients died by the first 100 day on study at the interim analysis (Nov 15 2005 cut-off) and 5% died by the first 100 day at the clinical up date (Apr 3 2006 cut-off), all due to disease progression. The fatal AEs reported on lapatinib combination arm were 2% and occurred after 100 days on study, most related to the tumor progression.

Seven patients (4%) in lapatinib + capecitabine combination arm experienced a decreased LVEF during the study but all were resolved without sequelae. Two of these were grade 1, three were grade 2, and one was grade 3 and one reported without grade. All seven events in the lapatinib + capecitabine group were considered drug related by the investigator, versus two drug-related LVEF events on the capecitabine alone control arm. Five of the seven events in the lapatinib + capecitabine group were asymptomatic (grade 2 or less). None of these was fatal or lead to treatment termination. QT prolongation has been observed pharmacokinetic QT study, but no case of Torsade De Pointes has been reported (detailed in clinical pharmacology review).

1.3.4 Dosing Regimen and Administration

The proposed dose of TYKERB is 1,250 mg (5 tablets) once daily (continuously) in combination with capecitabine 2,000 mg/m^2/day (administered orally in 2 doses approximately 12 hours apart) on days 1-14 in a 21 day cycle.

The dose of lapatinib should not be divided and given more than once daily. This would increase the AUC of lapatinib and possibly greater toxicity

1.3.5 Drug-Drug Interactions

Clinically relevant concentrations of lapatinib inhibit all of the CYP enzymes tested with an I/Ki ratio > 0.1. The strongest CYP inhibition was observed for CYPs 2C8 (I/Ki = 9.2) and 3A4 (I/Ki = 5.0). Lapatinib also inhibits P-gp with an I/IC_{50} of 1.4.

Lapatinib exposure were reduced by 72% after CYP3A4 induction by carbamazepine, and increased to 3.6 times control after CYP3A4 inhibition by ketoconazole.

In FDA clinical pharmacology reviewer's opinion, the applicant's ketoconazole inhibition study on lapatinib could not support a complete conclusion of the major route of CPYP450-mediated metabolism in humans is mainly CYP3A-4 and CYP3A5 with minor contributions from CYPs 2C8

and 2C19. The clinical consequence of the drug-drug interaction could not be observed reported in the breast cancer clinical studies submitted in this NDA application, because all known CPY3A4 inhibitor and inducer were prohibited from the studies. Post marketing clinical monitoring and follow up for lapatinib will be required.

1.3.6 Special Populations

As 87% (274/316) patients in the safety population were less than 65 years of age, no meaningful statistical comparison could be made by age (< 65 years versus ≥ 65 years). Similarly, 90% (290/316) patients in the safety population were white; no meaningful statistical comparison could be made by race (white, black, Asian, American Indian, Hispanic and other).

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Established Name: Lapatinib ditosylate (lapatinib)
Proprietary Name: Tykerb

Applicant: GlaxoSmithKline
2301 Renaissance Boulevard
P.O. Box 61540
King of Prussia, PA
19406-2772

Drug Class: Molecular targeted antineoplastic small molecule.

Description: Lapatinib is an orally administered, small-molecule, reversible, tyrosine-kinase inhibitor (TKI) that targets both ErbB1 (EGFR) and ErbB2 (HER2) receptors.

Chemical Class: Lapatinib ditosylate is a new molecular entity under US patents #6391874, #6713485, #6727256, and #6828320. The IUPAC name for lapatinib (GW572016F) is N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methylsulfonyl)ethyl]amino}methyl)-2-furyl]quinazolin-4-amine bis(4-methylbenzenesulfonate) monohydrate. The CAS registry number is 388082-78-8. An ATC Code has not yet been allocated by the WHO.

Proposed indication: Tykerb, in combination with capecitabine, is indicated for the treatment of patients (≥ 18 years) with advanced or metastatic breast cancer whose tumors overexpress HER2 (ErbB2)

Proposed Dosing Regimen: The proposed dose of TYKERB is 1,250 mg (5 tablets) once daily (continuously) in combination with capecitabine 2,000 mg/m^2/day (administered orally in 2 doses approximately 12 hours apart) on days 1-14 in a 21 day cycle.

2.2 Currently Available Treatment for Indications

Palliative chemotherapy is used for patients with advanced or metastatic breast cancer who have received prior therapy that include trastuzumab, anthracycline and taxane. These include:

- Single agent with trastuzumab, such as capecitabine, gemcitabine or vinorelbine + trastuzumab, or
- Single agent alone, such as vinca alkaloids, platinum, methotrexate or mitomycine C, or
- Combination of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF).
- Multiple other therapies such as gemcitabine, infusional 5-FU, and hormonal therapy.

2.3 Availability of Proposed Active Ingredient in the United States

Lapatinib has never been marketed in US or other region of the world.

2.4 Important Issues with Pharmacologically Related Products

No efficacy data of EGFR tyrosine kinase inhibitors or EGFR monoclonal antibodies has led to an approval in an indication for breast cancer.

Severe or lethal pulmonary toxicity (interstitial pneumonitis) and treatment acquired drug resistance has been reported in NSCLC patients treated with other small molecule EGFR inhibitors (gefitinib and erlotinib).

The dose limiting toxicity of lapatinib (1500 mg/day) in combination with capecitabine (2000 mg/m^2/day) was rash and diarrhea.

2.5 Pre-submission Regulatory Activity

IND: Lapatinib IND 61362 was submitted on December 6, 2000, FDA accepted this IND with recommendations on implement a validated criteria and detailed EGFR inhibitor specific monitoring plan for toxicity evaluation, as well as selecting a physician as the principle investigator.

EOP2 Meeting: An EOPS meeting was held on May 5, 2003, FDA advised the sponsor to clearly define the targeting patient population, i.e., the prior chemotherapy and submit the indented registry protocol for SPA review.

Special Protocol Assessment: The pivotal Phase III study supporting use of lapatinib in combination with capecitabine (EGF100151) was submitted for a Special Protocol Assessment; FDA responses were provided to applicant on 21 November 2003. FDA recommended that the study show be powered for survival and in combination with capecitabine; the patient population should be the refractory breast cancer patients indicated in capecitabine label.

Fast Track Designation: lapatinib received Fast Track designation on 28 October 2003 for the treatment of patients with refractory advanced or metastatic breast cancer who have ErbB2 overexpression [redacted]

Emergent teleconference: On March 23 2006, the sponsor requested an emergent teleconference with FDA to communicate the result of study EGF100151 interim analysis and IDMC's recommendation of stopping study. FDA did not make any comments.

Pre-NDA Meeting: A pre-NDA meeting was held with your Division on 26 May 2006. As agreed, the indication was to be based on results from study EGF100151. The applicant was to be providing a rolling submission to initiate review of the application. As agreed between FDA and applicant, additional clinical data from Study EGF100151 were to be submitted as an NDA amendment during the first 60 days after completion of the Rolling NDA. These data are from an updated dataset that includes efficacy and safety data up to 3 April 2006. A four-month safety update also were to be submitted as per 21CFR314.50 (d) (5) (vi) (b).

2.6 Other Relevant Background Information

None

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Lapatinib is a small molecule and a member of the 4-anilinoquinazoline class of kinase inhibitors. The chemical name for lapatinib is N-(3-chloro-4-{[(3-fluorophenyl)methyl]oxy}phenyl)-6-[5-({[2-(methylsulfonyl)ethyl]amino}methyl)-2-furanyl]-4-quinazolinamine bis(4-methylbenzenesulfonate) monohydrate. It has the molecular formula C29H26ClFN4O4S (C7H8O3S)2 H2O and a molecular weight of 943.5. Lapatinib ditosylate has the following chemical structure:

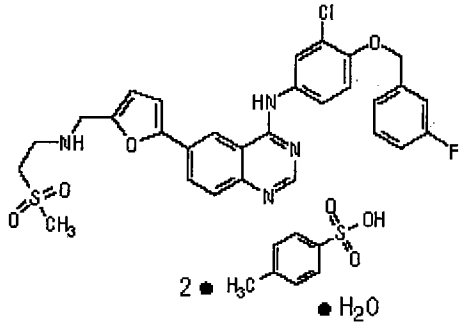


Figure 2: Lapatinib ditosylate chemical structure.

Lapatinib is a yellow solid, and its solubility in water is 0.007 mg/mL and in 0.1N HCl is 0.001 mg/mL at 25□C.

Each 250-mg tablet of TYKERB contains 405 mg of lapatinib ditosylate monohydrate, equivalent to 250 mg lapatinib freebase or 398 mg as lapatinib ditosylate per tablet.

The inactive ingredients of TYKERB are Tablet Core: Magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate. Coating: Orange film-coat: FD&C yellow No.

6/sunset yellow FCF aluminum lake, hypromellose, macrogol/PEG 400, polysorbate 80, titanium dioxide.

The application is recommended for approval with respect to the chemistry, manufacturing, and controls (CMC). However, this recommendation assumes that the pharmacology/toxicology team finds the applicants drug substance and drug product impurities acceptance criteria to be acceptable from a safety perspective (pending review for 22-SEP- 2006, consult request). An unacceptable recommendation from the pharmacology/toxicology team may have implications with regard to the drug substance and drug product impurities acceptance criteria and/or the retest and expiration dating periods, respectively.

Although the applicant has not responded to Comments 5-7 of the 06-DEC-2006, IR letter, the comments are not considered approvability issues, as they do not affect the overall quality assurance of the product. These comments are intended to gain further product knowledge and process understanding from the applicant under the ONDQA pilot program. They can be addressed post-approval due to the short review timeline.

The following comments and risk management statements regarding CMC should be included in the action letter:

- As indicated in our teleconference on November 16, 2006, your proposed CMC Regulatory Agreement submitted as part of the CMC Pilot Program is under review. Your proposal outlines the regulatory mechanisms for managing changes related to process design and control spaces post-approval. While a mutually accepted CMC Agreement is not a condition for the approval of this application, it will have implications for post-approval changes. Therefore, you are reminded that, until the CMC Agreement is approved, the existing regulations and guidances should be followed, as appropriate for the post approval CMC changes.

- We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be

3.2 Animal Pharmacology/Toxicology

The non-clinical studies with oral lapatinib support the safety of its use in metastatic breast cancer. Two-year carcinogenicity studies with lapatinib are ongoing. The toxicology review is summarized as below:

a) The nonclinical findings have shown the target sites of toxicity with lapatinib to be gastrointestinal, hepatobiliary, adrenal and dermatological. Many of these toxicities are seen in the clinic and are direct effects of the pharmacology of lapatinib.

b) Lapatinib was not mutagenic or clastogenic in the in vitro and in vivo assays studied. An impurity present in the formulation of lapatinib at levels exceeding recommended levels for genotoxic impurities tested positive for genotoxicity in two in vivo assays.

c) Lapatinib did not impair fertility when administered to either male or female rats prior to and during the mating period. There were no effects on male or female rat, mating or fertility at doses up to 120 mg/kg/day in females and 180 mg/kg/day in males (approximately 6.4 times and 2.6 times the expected human clinical exposure based on AUC, respectively).

d) Lapatinib was not teratogenic in either the rat or the rabbit. Lapatinib was studied for effects on embryo-fetal development in pregnant rats and rabbits given oral doses of 30, 60, and 120 mg/kg/day. There were no teratogenic effects; however, minor anomalies (left-sided umbilical artery, cervical rib and precocious ossification) occurred in rats at the maternally toxic dose of 120 mg/kg/day (approximately 6.4 times the human clinical exposure based on AUC). In rabbits, lapatinib was associated with maternal toxicity at 60 and 120 mg/kg/day (approximately 0.07 and 0.2 times the human clinical exposure, respectively, based on AUC) and abortions at 120 mg/kg/day. Maternal toxicity was associated with decreased fetal body weights and minor skeletal variations.

e) Lapatinib did lead to a dramatic increase in neonatal loss in rats during the first week of life. Studies were conducted to examine the effects of lapatinib on embryo-fetal as well as pre- and postnatal development. In a study where pregnant rats were dosed with lapatinib during organogenesis and through lactation, a decrease in pup survival occurred between birth and postnatal day 21 at doses of 60 mg/kg/day or higher (approximately 3.3 times the human clinical exposure based on AUC). At a dose of 120 mg/kg/day (approximately 6.4 times the human clinical exposure based on AUC) 91% of the pups had died by the fourth day after birth, while 34% of the 60 mg/kg/day pups were dead. The highest no-effect dose for this study was 20 mg/kg/day (approximately equal to the human clinical exposure based on AUC).

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The primary evidence of the efficacy and safety of lapatinib in combination with capecitabine is provided by the interim analysis of the randomized study EGF100151 (the study was closed to enrollment following the results of the interim analysis). This study was conducted in women with ErbB2 overexpressing advanced or metastatic breast cancer who had received prior anthracyclines, taxanes and trastuzumab.

To support the randomized study, the efficacy and safety results from three supportive studies are also summarized (Study EGF20002, Study EGF20008 and Study EGF10005). The two non-controlled lapatinib monotherapy studies (Study EGF20002, Study EGF20008) were conducted in women with advanced or metastatic ErbB2-positive breast cancer whose disease had progressed while receiving trastuzumab-containing regimens (except cohort B of EGF20008 which enrolled subjects with ErbB2 non-overexpressing breast cancer and who had not received trastuzumab). Supportive efficacy data are also observed in the dose escalation phase I study EGF10005; lapatinib

in combination with capecitabine was studied in male and female patients with solid tumors. Among them, seven subjects (16%) had advanced/metastatic breast cancer.

4.2 Tables of Clinical Studies

Table 2: List of clinical study reviewed

Orders	Protocol ID	Design	Relevance
Key study	EGF 100151	This is a randomized, open-label, multicenter study comparing lapatinib plus capecitabine versus capecitabine alone in women with ErbB2 overexpressing advanced or metastatic breast cancer. The primary objective of the study was to evaluate and compare time to progression. Secondary endpoints were overall survival, response rate, progression free survival, and response duration.	Efficacy Safety
Supportive studies	EGF 20002	This is an open-label, multicenter, single arm study of oral lapatinib in women with advanced or metastatic breast cancer whose disease had progressed while receiving trastuzumab containing regimens. The primary objective of the study was to evaluate the tumor response rate (complete or partial response).	Efficacy Safety
	EGF 20008	This was a uncontrolled, open-label, two-cohort, multicenter study to evaluate the efficacy and toxicity of oral lapatinib administered to female subjects with refractory advanced (Stage IIIb) or metastatic (Stage IV) breast cancer. The primary objective of this study was to evaluate tumor response rate (complete or partial) in two cohorts of advanced or metastatic breast cancer subjects treated with oral lapatinib. Cohort A were to have ErbB2 overexpressing tumors and Cohort B were to have non- ErbB2 overexpressing tumors.	Efficacy Safety
	EGF 10005	This was an open-label, multiple-dose, dose-escalation study of oral lapatinib and oral capecitabine given in combination to male and female subjects with advanced solid tumors, with a life expectancy of more than 12 weeks. The primary objectives of the study were: safety, tolerability, and PK.	Safety PK

Source: NDA 22059

4.3 Review Strategy

This NDA clinical review is based primarily on the efficacy and safety data of EGF 100151, which are most relevant to the proposed indication. The electronic submission, with the CSRs, and other relevant portions of GEF 100151 were reviewed and analyzed. The study summary of EGF20002, EGF20008 and 10005 were also reviewed. The key review materials and activities are outlined as blow:

- The electronic submission of the sNDA;
- Relevant published literature for background information only;
- Relevant submissions in response to medical officer's questions;
- Sponsor presentation slides to FDA on Oct 10 2006;
- Major efficacy and safety analyses reproduced or audited by JUM program using raw data sets provided by the applicant;

- Electronic CT scans, bone scans, clinical photographs, and independent review documents;
- Other non-clinical review;
- Discussion's with consultants.

4.4 Data Quality and Integrity

A number of methods were utilized in order to evaluate the quality and integrity of the data from study EGF 100151 as outlined below:

Clinical inspections: The clinical inspection was focused on the study EGF 100151 since it provided the most crucial efficacy data for this NDA application. The Division of Scientific Investigations (DSI), Clinical Practice Branch I, conducted clinical inspection of two sites of study EGF 100151 as proposed by the reviewer, described in the table below.

Table 3: Reviewer proposed EGF100151 study sites to be investigated by the DSI

Indication		Lapatinib in combination with capecitabine for the treatment of women with refractory advanced or metastatic breast cancer who have ErbB2 over expression) and who have received prior therapy which included anthracyclines, taxanes, and trastuzumab	
Protocol #		EGF100151	
Study Title		A Phase III, Randomized, Open-Label, Multicenter Study Comparing GW572016 and Capecitabine (Xeloda) versus Capecitabine in Women with Refractory Advanced or Metastatic Breast Cancer	
Site Number/ Address		91482	91450
		Nottingham City Hospital Department of Clinical Oncology Next to Fraser Ward H Block 1st Floor Hucknall road Nottingham NG5 1PB, UK	ZOZ MSWiA z Warminsko Mazurskim Centrum Onkologii Onkologii w OlsztynieOddzial Chemioterapii Ul. Wojska Polskiego 37 10-228 Olsztyn, Poland
PI ID / Name		043954 / Dr. Stephen Chan,	040529/ Dr. Agnieszka Jagiello-Gruszfeld
Enrollment Number		13	11
CR + PR	**IRC**	2	3
	INV	4	3
TTP Events	**IRC**	5	6
	INV	7	3
OS Events		3	3
Subject ID	**Cape[1]**	493, 1115, 1118, 1119	111, 114, 130, 134, 1261
	Lap + Cape[2]	490, 494, 1116, 1117, 1123, 1124, 1125, 1126, 1338	113, 115, 128, 129, 132, 133

1. Capecitabine 2500 mg/m^2/day
2. Lapatinib 1250 mg/day + capecitabine 2000 mg/m^2/day

A number of factors were considered for site selection, including accrual numbers, data documentation, number of responses (CRs and PRs), number of progression events and deaths and the discrepancy between investigators and IRC assessments regarding the number of responses and progression events.

To ensure that close to 10% study subjects' records of study EGF100151 to be audited, the DSI consultant, Dr. Lauren Iacono-Connor, proposed following with two additional US study sites (92434 and 90906) to be investigated (see table below).

Table 4: Additional US sites of study EGF100151 to be audited

PI ID / Name	Site Number/ Address	Enrolled N (CL/C)	IRC TTP / INV TPP / OS Events
14344 / Dr. Sandra Franco	92434 / Memorial Regional Cancer Center Hollywood, Florida	4 (3/1)	4 / 3 / 1
68711 / Dr. Mamta Kalidas	90960 / Baylor college of Medicine Houston, Texas	4 (1/3)	2 / 3 / 0

IRC = independent review committee, INV = investigator, TTP = time to progression, OS = overall survival.

The first two sites (92434 and 90906) have discrepancy in TTP events determination between the independent review committee and investigators. Although both parties agree on the TTP event for subjects at the third study site (90597), the independent review committee did not agree with the investigator on the event date (44-day difference).

In addition, the DSI also visited the applicant head quarter (GlaxoSmithKline, King of Prussia, PA) and independent review agency to assessment the study conduct and data handling. The inspectors of DSI found that the clinical investigators were generally found to be adequate in the execution of the studies identified for audit. The studies were found to be well controlled and well documented. However, several regulatory deviations were observed. Consistent with the routine clinical investigator compliance program assessments the inspection focused on compliance with protocol inclusion/exclusion criteria and consistency of efficacy data found in source documents with that reported by the sponsor to the agency. CRFs were assessed for data consistency with the source documents. AEs and SAEs were properly documented and reported to the sponsor and to the IRB in a timely manner. A Form FDA 483 was issued citing 2 observations.

Observation 1. The investigation was not conducted in accordance with the investigational plan. Specifically, Subjects 761 (LM) and 762 (YB) did not have the weekly assessment for the first two weeks of the study (hemoglobin, hematocrit, red blood cell count, white-blood cell count with differential and platelet count); hematology test. There is no documentation of waiver from the sponsor as to acceptance of the deviation for continuing the study subjects in the study.

Observation 2. Failure to obtain informed consent in accordance with 21 CFR Part 50 from each human subject prior to conducting study-related tests. Specifically, a new version of the informed consent dated June 25, 2005 was approved by the IRB on 8/8/05. The version incorporated the risk of neutropenia. Subject 759 (VF) signed this version on 04/12/06. She was taken off the study on 10/19/05.

The medical and statistical reviewers have conducted independent efficacy and safety analyses based on the primary data submitted in SAS transport format and the JMP counterpart. Any discrepancies between the reviewers' results and those of the sponsor are disclosed in relevant sections of this joint medical/statistical review.

An imaging consult was requested to evaluated difference between the independent reviewer and investigators assessment.

Case report forms in electronic format were reviewed in selected patients. The CRF were randomly sampled at one per each country initially. Problem oriented samplings on specific files were used along the review process. About 300 CRFs of study EGF100151 were reviewed in various details.

4.5 Compliance with Good Clinical Practices

The study were generally followed good clinical practice. The number of patients without consent, or not fit for enrollment criteria were less than 5% in study EGF 100151. Some of these problems were identified in DSI audit (see section 4.4 for details).

4.6 Financial Disclosures

Conflicts of interest of investigator would be considering factor if there were any claim. There were two claims of conflicts of interest for study — each investigator, one from a site at — and the other from a site at — , enrolled —patients (<1%, n = —. Although there was no analysis conducted to explore the effect of these sites' data, the likelihood of potential bias may introduce by two patients from different study sites in a 399 patients study analysis is low. Approximately 500 investigators (128 study sites) who did not provide financial disclose have not enrolled any patients in study —

There were two claims of conflicts of interest for study — each investigator, one from a site at — and the other from a site at — , each enrolled —patients (<1%, n = —. Although there was no analysis conducted to explore the effect of these sites' data, the likelihood of potential bias may introduce by two patients from different study sites in a 399 patients study analysis is low.

1 — investigator at —
— , in study —

No analysis was conducted to explore the effect of this site's data on the results of study — as this site enrolled — of the — patients (<1%) in the ITT population used in the analysis of this study, and therefore does not have the potential to bias the outcome and/or conclusions of the study.

2. — investigator at —
— in study —

No analysis was conducted to explore the effect of this site's data on the results of study EC — as this site enrolled — of the — patients (<1%) in the ITT population used in the analysis of this study, and therefore does not have the potential to bias the outcome and/or conclusions of the study.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Absorption: Absorption following oral administration of lapatinib is incomplete and variable. Serum concentrations appear after a median lag time of 0.25 hours (range 0 to 1.5 hour). Peak plasma concentrations (Cmax) of lapatinib are achieved approximately 4 hours after administration. Daily dosing of lapatinib results in achievement of steady state within 6 to 7 days, indicating an effective half-life of 24 hours.

At the dose of 1,250 mg daily, steady state geometric mean (95% confidence interval) values of Cmax were 2.43 mcg/mL (1.57 to 3.77 mcg/mL) and AUC were 36.2 mcg.hr/mL (23.4 to 56 mcg.hr/mL).

Divided daily doses of LAPATINIB resulted in approximately 2-fold higher exposure at steady state (steady state AUC) compared to the same total dose administered once daily.

Systemic exposure to lapatinib is increased when administered with food. Lapatinib AUC values were approximately 3- and 4-fold higher (Cmax approximately 2.5- and 3-fold higher) when administered with a low fat (5% fat-500 calories) or with a high fat (50% fat-1,000 calories) meal, respectively.

Distribution: Lapatinib is highly bound (>99%) to albumin and alpha-1 acid glycoprotein. In vitro studies indicate that lapatinib is a substrate for the transporters BCRP (ABCG1) and p-glycoprotein (ABCB1). Lapatinib has also been shown in vitro to inhibit these efflux transporters, as well as the hepatic uptake transporter OATP 1B1, at clinically relevant concentrations. Lapatinib is a P-glycoprotein (P-gp) substrate with an efflux ratio of 15.6 at a concentration that approximates steady-state Cmax.

Metabolism: Lapatinib undergoes extensive metabolism, primarily by CYP3A4 and CYP3A5, with minor contributions from CYP2C19 and CYP2C8 to a variety of oxidated metabolites, none of which accounts for more than 14% of the dose recovered in the feces or 10% of lapatinib concentration in plasma. Lapatinib exposure were reduced by 72% after CYP3A4 induction by carbamazepine, and increased to 3.6 times control after CYP3A4 inhibition by ketoconazole.

Systemic exposure to lapatinib was increased 14% in moderate and 63% in severe hepatic impairment.

Elimination: At clinical doses, the terminal phase half-life following a single dose was 14.2 hours; accumulation with repeated dosing indicates an effective half-life of 24 hours.

Elimination of lapatinib is predominantly through metabolism by CYP3A4/5 with negligible (<2%) renal excretion. Recovery of parent lapatinib in feces accounts for a median 27% (range 3 to 67%) of an oral dose.

Effects of Age, Gender or Race: Studies of the effects of age, gender or race on the pharmacokinetics of lapatinib have not been performed.

5.2 Pharmacodynamics

Mixed-effects modeling of the Fridericia corrected QT interval (QTcF) indicated a significant relationship between lapatinib concentration and the QTcF interval. Based on the model parameters, the predicted change in QTcF was estimated at peak concentrations following the recommended dose of lapatinib (1250 mg/day in combination with capecitabine).

- At the mean peak concentration (Cmax) of 3203 ng/ml following the 1250 mg daily dose, the predicted change in QTcF was estimated to be 13.5 msec (ICH recommend up linit is 10 msec).
- Using the upper 95% confidence limit of the slope estimate, the predicted QTcF prolongation at the mean Cmax was estimated to be 23.4 msec.

Additionally, factors that could increase lapatinib concentrations, such as co-administration of CYP3A4 inhibitors, administration of drug with food, or administration to patients with hepatic impairment, would be expected to further prolong the QTc interval.

5.3 Exposure-Response Relationships

Clinical studies assessing the relationships between exposure and efficacy as well as between exposure and safety were not performed. . Pharmacokinetics data were not collected in Study EGF100151. The basis of the proposed dosing recommendations is as below.

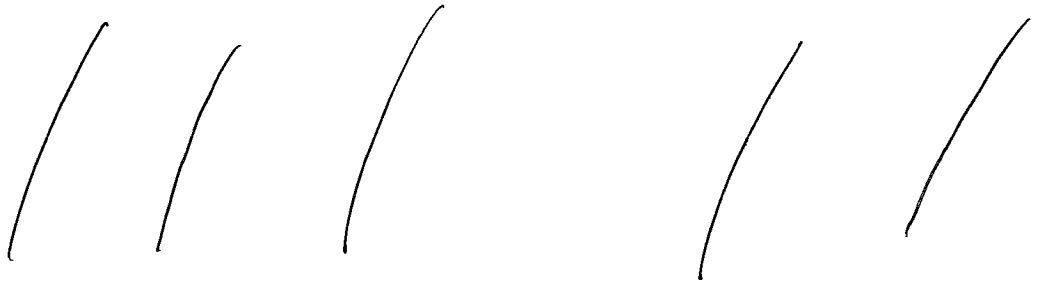
The recommended dose for the combination arm for the study EGF 100151 was based on data from Study EGF1005, a Phase I safety and tolerability study in which lapatinib was administered with capecitabine. The 1250/2000 regimen was identified as the "optimum treatment regimen (OTR)" based upon empirical consideration of tolerability. The OTR was defined as the dose of lapatinib and capecitabine at which no more than 1 of 6 subjects experienced a dose-limiting toxicity (DLT). The DLTs that determined the OTR were grade 3 diarrhea and grade 3 rash. Although the approved capecitabine dose is 2500mg/m2/day, the clinical trial data submitted for the regulatory approval of capecitabine included dose modification, either a dose reduction or interruption, in 55% of the subjects. Thus the data used for capecitabine approval included a substantial number of subjects who received 2000mg/m2/day.

In addition, the safety profile of lapatinib in combination with capecitabine is not truly comparable to the capecitabine alone arm, since the capecitabine dose for the control arm is 25% higher (2000 mg/m^2 vs. 2500 mg/m^2). The details are describe in section 6 and 7.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication for Previously Treated, Her2 Overexpressing, Advanced or Metastatic Breast Cancer

Proposed indication: Tykerb, in combination with capecitabine, is indicated for the treatment of patients (≥ 18 years) with advanced or metastatic breast cancer whose tumors overexpress HER2 (ErbB2)



6.2 Methods

This review is focused on the following items:

- Whether the study conduct and data collection were followed study design and statistical plan
- The impact of each amendment to the study
- The validity of the interim analysis and clinical update for TTP.
- The data collection and assessment for the primary endpoint, TTP, including the quality, time and interval of the tumor assessments, CRF documentation, data entry, data interpretation and data process.
- The reason for the discrepancies of TTP improvement between the interim analysis and clinical update analysis, as well as the independent review and investigators analysis.
- The validity of the other efficacy results.

6.3 General Discussion of Endpoints

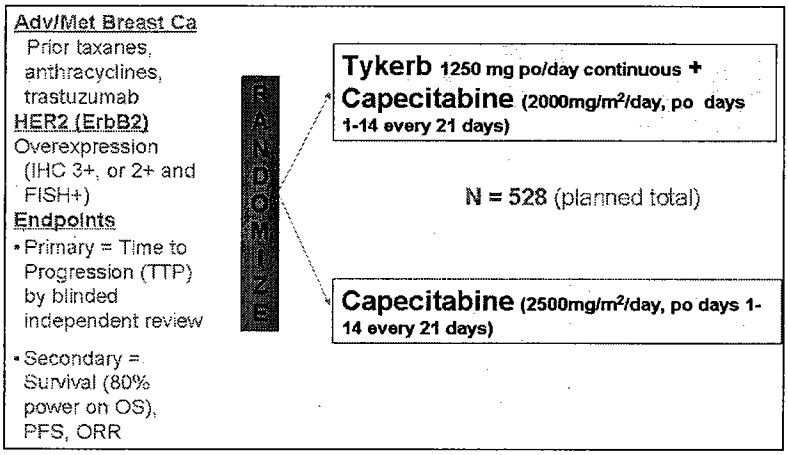
The study EGF 100151 is titled "A Phase III, Randomized, Open-Label, Multicenter Study Comparing GW572016 and Capecitabine (Xeloda) versus Capecitabine in Women with Refractory Advanced or Metastatic Breast Cancer". The original primary efficacy endpoint of study EGF 100151 was time to progression (TTP) defined as the interval between the date of randomization and the earliest date of disease progression. The protocol also includes treatment termination because clinical deterioration and death due to breast cancer as part of the TTP events (detailed in sections 6.1.3.4.2 and 10.1.1.1.8). Since the TTP events included radiological disease progression, symptomatic disease progression, and death, it is similar to progression free survival. At the time of special protocol assessment, FDA recommended that the sponsor should use only radiological and death events for this primary endpoint measurement and exclude the symptomatic disease progression. The applicant required copies of all radiological scans performed during the study, including at the time of discontinuation of investigational therapy, for all subjects. The applicant were to arrange for independent, blind review of all radiological scans and medical photographs to have a independent and blind assessment of TTP events, objective progression and breast cancer death, to reduce potential bias from investigators' assessment. The applicant also increased enrollment sample size (372 to 528 subjects) to power the study for secondary endpoint, overall survival.

6.4 Study Design

6.4.1 General Design and Treatment Plan

This was a randomized, open-label, multi-center study to evaluate and compare the treatment of lapatinib + capecitabine versus capecitabine alone administered to women with advanced or metastatic breast cancer overexpressing ErbB2, who have received prior therapy which included anthracyclines, taxanes (for adjuvant and/or metastatic disease) and trastuzumab (for advanced / metastatic disease). Subjects had measurable disease as defined by response evaluation criteria in solid tumors (RECIST).

Figure 3: Study Design and Treatment Plan



Approximately 372 female subjects (186 in each arm) were to be enrolled originally, and amendment 5 expanded sample size to 528 to power for the secondary study endpoint, overall survival. Subjects were to be randomized to one of two treatment arms, to receive treatment described in table below.

Table 5: Treatment plan

Arms	Capecitabine + Lapatinib Combination	Capecitabine
Capecitabine	2000 mg/m^2/day, administered at 1000 mg/m^2 q 12 hr x 28, every 21 days	2500 mg/m^2/day, administered at 1250 mg/m^2 q 12 hr x 28, every 21 days
Lapatinib	1250 mg/day PO continue	None

Note: The dose modification is described in the section 10.1.1.1.5.

Randomization was to be stratified according to the following:

1. Stage of Disease
   - Stage IIIB
   - Stage IV

2. Site of disease were to be assigned to 1 of 2 categories:
   - Visceral
   - Non-visceral

Treatment was to be administered until disease progression or withdrawal from study due to unacceptable toxicity or other reasons (i.e., consent withdrawal, non-compliance, etc.).

Clinical and laboratory parameters were to be assessed to evaluate disease response and toxicity of randomized therapy. Safety and efficacy assessments were to be performed every 6 weeks for the first 24 weeks, then every 12 weeks and at the end of treatment. Additional safety assessments were to be performed on all subjects every 3 weeks and at the end of treatment. Subjects withdrawn from

investigational drug who had not progressed were to be assessed every 12 weeks until progression. Thereafter, subjects were to be followed for survival at approximately 12-week intervals until death.

Amendment 7, May 12, 2006, was made due to termination of the study. Based on IDMC recommendation after reviewing interim analysis results, the study was closed to new subject enrollment because of positive results. The control arm patients are allowed to crossover after disease progression starting Apr 3 2006. The study will proceed in two phases. The first phase will lead to an evaluation of the primary endpoint of time to progression. Then the study will move into a follow-up phase, at the end of which there will be an analysis of mature overall survival data. The applicant has notified FDA about IDMC's recommended actions and this amendment.

6.4.2 Eligibility Criteria

The complete eligibility criteria are detailed in section 10.1.1.1.6, and major eligibility criteria were as follows:

- Histologically or cytologically confirmed invasive breast cancer (stage IIIb or IV disease)
- Documentation of ErbB2 overexpression (IHC 3+ or IHC 2+ with FISH confirmation) based on local laboratory or initial diagnostic results. Where testing is not feasible, central laboratory testing were to be utilized
- Documented progression of advanced or metastatic breast cancer defined as appearance of any new lesion not previously identified or increase of 25% or more in existent lesions.
- Refractory breast cancer defined as progression in the metastatic setting or relapse within 6 months of completing adjuvant therapy which must include:
    - an anthracycline
    - taxane-containing regimens
    - trastuzumab
    - No prior treatment with capecitabine is permitted
- Subjects with hormone receptor positive tumors, must have disease progression following hormonal therapy
- Female subjects must be ≥18 years of age
- ECOG Performance Status of 0 or 1
- Measurable disease according to RECIST
- Subjects must have archived tumor tissue available to re-evaluate intra-tumoral expression levels of ErbB1 andErbB2 by IHC and FISH testing performed by the study central laboratory. Central laboratory results will not be used to determine subject eligibility for the study, unless testing is being used for required documentation of ErbB2 overexpression.
- Life expectancy of ≥12 weeks
- Bisphosphonates should not be initiated following study entry
- Cardiac ejection fraction within the institutional range of normal as measured by echocardiogram (MUGA scan may be performed if ECHO is not available)
- Adequate renal, hematological and hepatic function.

6.4.3 Study population

Intent-to-Treat (ITT) population was initially proposed to include all randomized subjects who receive at least one dose of randomized therapy, and were to be used for the analysis of efficacy data. Amendment 2, May 24, 2004, as per FDA recommendation, the protocol revised ITT population to all randomized subjects.

The **Safety Population (SP)** was comprised all randomized subjects who receive at least one dose of randomized therapy, and were to be based on the actual treatment received, if this differs from that to which the subject was randomized.

6.4.4 Statistical Plan

6.4.4.1 Data Management

Withdrawal:

- Subjects were to be treated until disease progression or withdrawal from the study treatment due to unacceptable toxicity.
- Subjects may also withdraw from the study treatment for other reasons prior to disease progression or unacceptable toxicity.
- All withdrawals were to be included in analyses up to the time of withdrawal.
- Subjects who are withdrawn prematurely from investigational product, but who are not withdrawn from the study at the same time, were to be included in all analyses regardless of the duration of treatment.

Missing Data:

Efficacy assessments were scheduled at defined intervals of every 6 weeks for the first 24 weeks, then every 12 weeks and at the end of treatment. Subjects withdrawn from study who have not progressed were to be assessed every 12 weeks until progression and then followed for survival.

The duration of follow-up was to be depended on the treatment efficacy and toxicity of each subject. No imputation was to be allowed for missing data. Available data were to be summarized over specified intervals. For time-to-event endpoints, the last date of known contact was to be used for those subjects who have not reached the event at the time of the analysis; such subjects were to be considered censored in the analysis.

Reviewer: FDA generally does not permit inclusion of data where more than one consecutive tumor assessment visits are missing.

6.4.4.2 Endpoints

Primary Endpoint

The primary efficacy endpoint of Study EGF100151 was time to progression (TTP) as assessed by a blinded independent review committee (IRC) based on radiological imaging and medical photographic data. TTP was defined as the interval between the date of randomization and the earliest date of either disease progression or death due to breast cancer without prior progression.

Secondary Endpoints

- Overall survival was defined as the time from randomization until death due to any cause
- Progression-free survival was defined as the time from randomization until the first documented sign of disease progression or death due to any cause
- Six-month progression-free survival was defined as the percentage of surviving subjects who were progression-free six months after the date of randomization
- Overall tumor response rate was defined as the percentage of subjects achieving either a complete tumor response (CR) or a partial tumor response (PR)
- Clinical benefit was defined as the percentage of subjects with evidence of CR or PR or stable disease (SD) for at least 6 months
- Time to response was defined as the time from randomization until first documented evidence of CR or PR (whichever status is recorded first)
- Duration of response was defined as calculated in the subset of subjects who show CR or PR, to be the time from first documented evidence of CR or PR until the first documented sign of disease progression or death due to breast cancer, if sooner

6.4.4.3 Analyses

All comparisons between the lapatinib plus capecitabine combination, the testing arm, to the capecitabine alone, the control arm, were to be performed using ITT population. The study sample sized was increased from 372 to 528 subjects as per FDA recommendation to power the study for the secondary endpoint, overall survival.

Statistical hypothesis:
Null H_0: ≥ 1 or to reject it in favor of the alternative hypothesis
H_A: < 1, where is the hazard ratio for TTP: GW572016 + capecitabine / capecitabine alone.

A maximum of two analyses for TTP were to be occur after approximately 133 and 266 events (progressions or deaths due to breast cancer). O'Brien-Fleming stopping boundaries with one-sided 2.5% significance level will be used to reject either H0 (i.e. support for superior efficacy in the GW572016 plus capecitabine arm) or HA (i.e. support for inferiority or futility).

The planned key analyses are as follows:

Table 6: Analysis plan for key endpoints (pre-specified).

Analyses		Analysis and Event cut-off
TTP	Interim	In this study, there will be an interim analysis of TTP at 133 events. If the first analysis of TTP does not lead to early termination of the study for futility, then the study will continue to a second analysis of TTP at 266 events.
	Final	If this second analysis of TTP provides support for the superiority of GW572016 plus capecitabine, then the study will continue to recruit approximately 528 subjects.
OS		When 457 deaths have been observed, an additional analysis of the secondary endpoint of overall survival will be performed on the mature survival data. The study will have 80% power to detect a 30% increase in median survival time in subjects who receive GW572016 + capecitabine (10.4 months) compared to subjects who receive capecitabine alone (8 months).

Source: EGF100151 study report

Stopping rules:
An independent data monitoring committee (IDMC) will be convened to review accumulating safety and efficacy (time to progression) data and to provide an opportunity to terminate the study early if

- There are concerns regarding safety

- There is strong evidence of superior efficacy of GW572016 plus capecitabine

- There is strong evidence that GW572016 plus capecitabine will fail to show superiority if the study was allowed to run to its planned completion.

Based on 133 events, the boundary for superiority will be crossed if the log-rank test results in $p \leq 0.0028$. The futility boundary will be crossed if $p > 0.3308$. If more than 133 events are reported at the time of the interim analysis, only the first 133 events will be considered.

Reviewer: The interim analysis for TTP led to IDMC's recommendation for early termination of the study. However, the applicant recalculated an O'Brian-Fleming superiority boundary of $p<0.0014$ for 114 event and $p<0.0019$ for 121 events (detailed in efficacy section of TTP analyses). Although this is acceptable, one would prefer use the prespecified boundary. Please see statistical review by Dr. Ko for details.
Disadvantages of study EGF100151 stopped early could cause decreased accuracy in primary analysis of TTP and losing the power on survival analysis. Furthermore, if the investigator determined a subject with disease progression, the subject will be off study and no further data will be collected for objective tumor assessment, **regardless the independent reviewer opinion**. Then with the composite TTP endpoint (objective disease progression and breast cancer death), the independent reviewer will call the TTP event at whenever the death occurs, this may lead to over estimate treatment effect for both arms assuming the errors are balanced distributed.

6.4.5 Discussion

Reviewer: The design of study EGF 100151 is adequate and well controlled to evaluate the examine effectiveness for the proposed indication. The eligibility criteria and targeted patient population were acceptable for the proposed indication. The combination regimen chosen for the testing arm based on the results of the phase 1/2 studies is adequate. The choice of control group, capecitabine alone was suitable for the proposed patient population. The primary and secondary endpoints were set to provide a reasonable assessment of benefit. The implementation of independent, blind review was set to minimize potential bias in an open-labeled study. The prospective statistical analytic plan was acceptable in principle.

6.5 Efficacy Findings of Study EFR 100151

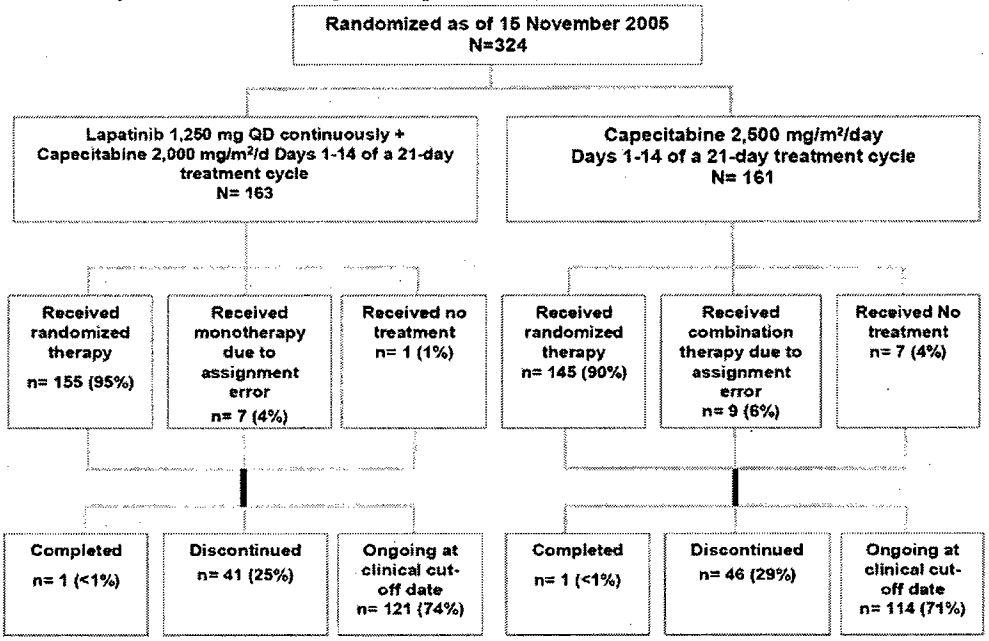
6.5.1 Patient Demography and Characteristics

Study Period: The first subject was randomized on March 29, 2004. The protocol defined interim analysis was conducted with a clinical cut off date of November 15, 2005. On 20 March 2006, the IDMC, based on this interim analysis, suggested that the results justified halting further enrollment into the study per protocol and that subjects in the capecitabine group be informed of results and given the opportunity to receive lapatinib + capecitabine. Therefore, GSK terminated subject enrollment on 03 April 2006.

The results from the interim analysis on all subjects enrolled between 29 March 2004 and 15 November 2005 was the primary component of the NDA study reports. FDA asked applicant to submit an efficacy update along with the safety update. The analysis of data up to 03 April 2006 was submitted in a subsequent NDA amendment.

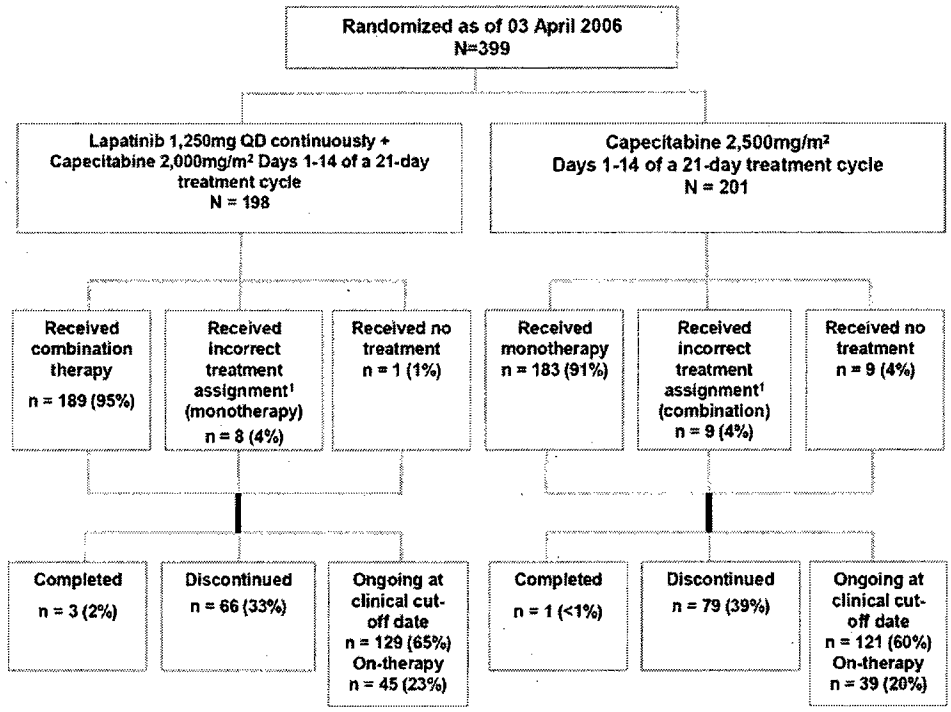
This was a global study conducted at 128 centers. The majority of subjects were enrolled within the European Union (54%) and United States (21%). Up to 15 November 2005 and 3 April 2006, 324 and 399 female subjects with advanced or metastatic breast cancer were randomized in the study, respectively. The patient disposition and accountability were as the figure and table below.

Figure 4: Study EGF100151 subject disposition (ITT, Nov 15 2005 cut-off)



Source: EGF100151 study report.

Figure 5: Study EGF100151 subject disposition (ITT, Apr 3 15 2006 cut-off)



Source: EGF100151 study report.

Study EGF 100151 all deviations including incorrect treatment and major protocol violations are summarized as below and the detailed in section 10.1.1.2.

Table 7: Protocol deviations occurred during study EGF 100151 (ITT).

	Nov 15 2005 Cut-off		Apr 3 2006 Cut-off	
Any Deviation / Arm	LC N=163 (%)	C N=161 (%)	LC N=198 (%)	C N=201 (%)
Total[1]	17 (10)	31 (19)	18 (9)	33 (16)
Did not receive prior regimens of anthracycline or taxane or trastuzumab	7 (4)	16 (10)	7 (4)	13 (6)
Incorrect treatment received	7 (4)	9 (6)	8 (4)	9 (4)
No study medication received	1 (<1)	7 (4)	1 (<1)	9 (4)
No prior anti cancer medications for metastatic breast cancer	0	3 (2)	0	3 (1)
Received hormonal therapy after randomization	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Tumor ErbB2 non-overexpressing	1 (<1)	0	1 (<1)	0
Other inclusion/exclusion deviations	2 (1)	1 (<1)	3 (2)[2]	2 (1)[3]

1 Only one major deviation per subjects listed in this summary.
2. One subject was without ErbB2 overexpression and two subjects were without disease progression after prior therapy.
3. One subject for lack of disease progression after prior therapy and one subject for concurrent anti-cancer therapy other than capecitabine.
LC = Lapatinib + Capecitabine , C = Capecitabine alone
Source: Study EGF 100151 report.

Reviewer: As shown in the figures and the table above, seventeen patients 4% received treatment that was opposite to the treatment assigned by the randomization. This was due to a technical problem of the electronic randomization system, which resulted incorrect notification on assignment (Details see section 10.1.1.2). In addition, there were 6% patients had major protocol violation, as detailed in section 10.1.1.2.

For the analyses of study EGF 100151, the sponsor and this FDA reviewer used following population: The **ITT population** included all randomized subjects, the **safety population** included all randomized subjects who received at least one dose of randomized therapy and was based on the actual treatment received (if this differed from the randomized treatment). The **per-protocol population** included all the subjects in the ITT population who had no major protocol violations.

Although there were 4% patients received incorrect treatment and 6% patients had protocol deviations in the ITT population, the TTP analyses in safety and per-protocol populations showed that these violations did not affect the out come of primary efficacy analysis TTP (see section 6.1.4.2.1).

Table 8: Study EGF 100151 Analyses populations

Populations	Nov 15 2005 Cut-off			Apr 3 2006 Cut-off		
	Lapatinib + Capecitabine (%)	Capecitabine (%)	Total (%)	Lapatinib + Capecitabine (%)	Capecitabine (%)	Total (%)
All subjects	163	161	324	198	201	399
ITT Population	**163 (100)**	**161 (100)**	**324 (100)**	**198 (100)**	**201 (100)**	**399 (100)**
Not treated	1 (<1)	7 (4)	8 (2)	1 (<1)	9 (4)	10 (4)
Wrong treatment	7 (4)	9 (6)	16 (5)	8 (4)	9 (4)	17 (4)
Safety Population	**164 (101)**	**152 (94)**	**316 (98)**	**198 (100)**	**191 (95)**	**389 (97)**
Per-Protocol Population	146 (90)	130 (81)	276 (85)	180 (91)	168 (84)	348 (87)

1. Based on the actual treatment that patients received.
Data Source: Study EGF 100151

At the time of clinical update, 399 patients were enrolled in this study. The median age was 53 years and 14% were older than 65 years. Ninety-one percent were Caucasian. Ninety-seven percent had stage IV breast cancer, 48% were ER or PR +, and 95% were ErbB2 IHC 3+ or IHC 2+ with FISH confirmation. Approximately 95% of patients had prior treatment with a taxane, an anthracycline and trastuzumab (detailed in section 10.1.1.2).

6.5.2 Efficacy

EGF 100151 is an open-label study designed to meet regulatory standards for submission of an NDA. GSK and FDA have previously reached agreement through a Special Protocol Assessment (August 2003) on the primary endpoint of TTP based on objective disease progression. The primary analysis was based on a blind independent review of tumor assessments.

The first subject was randomized on March 29, 2004 and prospectively planned interim analysis was conducted after 133 TTP events assessed by investigators and later by the IRC (disease progression or death due to breast cancer prior to progression). The applicant reported range of the follow up at interim analysis was 1 to 90 weeks, median 45 weeks. Following their review of the interim analysis (20 March 2006) the Independent Data Monitoring Committee (IDMC) unanimously recommended termination of study enrollment, which took place on 03 April 2006. Following the IDMC recommendation based on result of TTP analysis, the protocol was amended so that subjects in the capecitabine monotherapy group were allowed to crossover to receive lapatinib + capecitabine combination.

6.5.2.1 Primary Endpoint: Time to Progression (TTP) in ITT population

This section describes the primary endpoint TTP was analyzed in ITT population by both independent review and investigator assessments at two cut off dates, the interim analysis (Nov 15 2005) and the clinical update (Apr 3 2004). The independent review is the prespecified primary analysis. The TTP sensitivity analyses were also conducted in safety and per-protocol population to

examine the impact of major protocol violations. Other sensitivity analyses were also conducted to answer why the magnitude of improvement observed in the independent reviewer's analysis at the interim analysis is much greater than the independent reviewer analysis at the update and the investigator's analysis at he interim and updated analyses.

6.5.2.1.1 TTP Interim Analysis (Nov 15 2005 cut-off)

The interim analysis cut off date was determined at 133 event plus a additional 10% by the investigator's assessment to ensure that the independent review assessment for primary TTP analysis were to be conducted at approximately 133 events. Using this assessment, 7 weeks improvement of median TTP in the lapatinib + capecitabine arm was observed (25.9 weeks compared to 18.9 weeks in the capecitabine arm); hazard ratio of 0.59, (95% CI: 0.42, 0.84, p-value = 0.00219) (Table below).

At interim analysis, 121 TTP events were identified by IRC in 324 subjects randomized at the cut off date. The IRC assessed TTP was statistically significant in favor of testing group, with a hazard ratio of 0.49 (95% CI: 0.34, 0.71, two-sided p-value = 0.00008). The IRC assessed median TTP in the lapatinib + capecitabine group was 36.7 weeks compared to 19.1 weeks in the capecitabine group, a 17 weeks improvement. The O'Brien Fleming (Pampllona-Tsiatis implementation) boundary for 121 TTP events was $p \leq 0.0038$ (two-sided), as shown in Table below and more details in section 10.1.1.3.

Table 9: Study EGF 100151 TTP interim analysis by IRC and investigator assessment (ITT, Nov 15 2005 cut-off)

	Independent Assessment		Investigator Assessment	
	Lapatinib + Capecitabine (N=163)	Capecitabine (N=161)	Lapatinib + Capecitabine (N=163)	Capecitabine (N=161)
Number of Events	49 (30)	72 (45)	59 (36)	74 (46)
Median TTP, weeks	36.7	19.1	25.9	18.9
HR [95% CI]	0.49 [0.34, 0.71]		0.59 [0.42, 0.84]	
p-value	0.00008		0.00219	

1. Hazard ratio of <1 indicates a lower risk with lapatinib + capecitabine compared to capecitabine.
2. Stratified log-rank test stratifying for stage of disease and site of disease at screening.
Source: Study EGF 100151 report.

In question of whether protocol violations, including subjects received treatment that they were not randomized to and subjects who randomized did not meet eligibility criteria, will affect the primary analysis results, TTP analysis by independent assessment were conducted in safety population (SP) for the groups of actual treatment that subjects received. In addition, TTP analysis by independent assessment is conducted in per-protocol population (TTP) for eligible patients that received actual treatment below.

Table 10: TTP analyses by IND assessment in SP population (Nov 15 2005 and Apr 3 2006 cut-off)

TTP	Nov 15 2005 cut-off N = 324			
	SP		PPP	
	LC N=164	C N=152	LC N=146	C N=130
# Events (%), progression and death due to breast cancer	52 (32)	68 (45)	45 (31)	61 (47)
Death due to other cause	0	4 (3)	0	4 (3)
Censored, follow up ended	10 (6)	7 (5)	9 (6)	6 (5)
Censored, follow up on going	102 (62)	73 (48)	92 (63)	59 (45)
Median TTP, weeks	36.9	17.9	36.9	17.9
Improvement in median TTP, weeks	19.0		19.0	
HR [95% CI]	0.45 [0.31, 0.65]		0.44 [0.30; 0.66]	
p-value	0.000004		0.00001	

Source: Study EGF 100151 report.

Reviewer: TTP analyses based on either IRC or investigator assessment, both crossed protocol predefined efficacy boundary for TTP analysis. Using data set provided with this NDA application, the reviewer TTP analyses by IRC assessment in ITT, SP and PPP all confirmed the applicant's results. These results indicate that the protocol violations in study EGF 100151 have minimal effect in the TTP analysis of intent to treat population. However, the substantial difference of improvement magnitude of TTP analyses between the IRC assessment and investigator assessment are of concern.

The applicant reported differences between the IRC and investigators assessment for TTP analysis of study EGF100151. The data was reviewed and summarized in two tables below.

Table 11: The difference between IRC and investigator TTP assessment of Study EGF100151 at interim analysis (ITT, Nov 15 2005 and Apr 3 2006 cut-off)

	Lapatinib+ Capecitabine N=163 (%)	Capecitabine N=161 (%)	Total N=324 (%)
	IA N=163 (%)		
Total Progression by IRC	**49 (30)**	**72 (45)**	**121 (37)**
Complete Agreement with INV	16 (33)	38 (53)	54 (45)
PD later by INV	8 (16)	4 (6)	12 (10)
PD earlier by INV	10 (20)	11 (15)	21 (17)
Censored by INV	15 (31)[1]	19 (26)	34 (28)
Total Censored by IRC	**114 (70)**	**89 (55)**	**203 (63)**
Complete Agreement with INV	60 (53)	54 (61)[2]	114 (56)
Censored later by INV	16 (14)	7 (8)	23 (11)
Censored earlier by INV	13 (11)	7 (8)	20 (10)
PD by INV	25 (22)	21 (23)	46 (23)

INV=Investigator
1. Includes two patients who died from causes other than breast cancer.
2. Includes four patients who died from causes other than breast cancer.
Data source: Study EGF 100151 report.

Table 12: The major reasons for difference between IRC and investigator TTP assessment of Study EGF100151 at interim analysis (ITT, Nov 15 2005 cut-off)

	Lapatinib + Capecitabine N = 163, n (%)	Capecitabine N = 161, n (%)	Total N = 324, n (%)
Major PD Events Different for TTP Analysis	**58 (35)**	**55 (33)**	**113 (34)**
Interpretation of Data only	23 (14)	21 (13)	44 (13)
Different Selection of Organ/Lesions only	10 (6)	12 (7)	22 (7)
Both Interpretation and Selection	15 (9)	12 (7)	27 (8)
Missing Data (baseline imaging, photos, clinical information)	7 (4)	5 (3)	12 (4)
INV PD event time was after protocol defied events (133)	3 (2)	5 (3)	8 (2)

INV=Investigator
Data source: Study EGF 100151 report.

Reviewer: As indicated in the table above, the complete agreement between IRC and investigators TTP event assessments was 52% (54 progression events + 114 censored events / 324 patients). The disagreement on TTP events between the IRC and investigators was about 25% (34 censors vs. PD + 46 PD vs. censor /324 patients). The disagreement on the time of TTP events was about 23% (12 PD later + 21 early + 23 censor later + 20 censor early / 324 patients). With overall 34% disagreement, the percentage of itemized disagreement appears to be evenly distributed in this open labeled study. The differences in interpretations appear to be acceptable and reasonably balanced between the treatment arms, as generally noted in the clinical trials. However, in this reviewer's exploratory analyses (section 6.1.4.2.2), these differences primarily due to missing data for the independent assessment, which resulted that the TTP improvement by independent assessment can not be accurately characterized.

The applicant provided all IRC TTP assessments (253/324 cases) electronically, including scans, pictures, IRC radiology measurements and assessment forms. This reviewer reviewed all IRC TTP assessments and found that these assessments are reliable. The reviewer selected 21 representative cases of IRC assessment that were different from the investigators assessment for FDA imaging consultants to evaluate (shown in Table 95). The selection was based on the representative difference between IRC and investigator including:
- Lesion assessments (whether there is a new lesion, lesion measurement and interpretation, and lesion selection),
- Event determination (PD or not),
- IRC oncologist disagreed with IRC radiologists review (only one case).

The imaging consultants indicated that it is frequently observed in clinical studies that the differences arise between the independent and investigator assessment of TTP. The primary reasons for differences were due to the different interpretation of the lesion measurements, new lesions or the selection of different lesions by reviewers. However, this assumption is based on that all the tumor evaluation are adequate and assessable by the independent review (IRC).

6.5.2.1.2 TTP Update Analysis (4/3/2006 update)

The applicant submitted a TTP analysis update using the Study 100151 termination date, April 3, 2006 as the cut off date. In 399 randomized study patients, blind independent reviewers identified 184 TTP events. The TTP analysis based on IRC was statistically significant in favor of combination arm with a hazard ratio of 0.57 (95% CI: 0.43, 0.77, two-sided p = 0.00013). According to the investigator analysis, the median TTP on the lapatinib + capecitabine combination arm was 23.9 weeks compared to 18.3 weeks on the capecitabine arm with a hazard ratio of 0.72 (95% CI: 0.56, 0.92, two-sided p = 0.00762, Table below and more details in section 10.1.1.3).

Table 13: Study EGF 100151 TTP analysis update based on IRC and investigator assessment (ITT, Apr 3, 2006 cut-off)

	Independent Assessment		Investigator Assessment	
	Lapatinib + Capecitabine (N=198)	**Capecitabine (N=201)**	**Lapatinib + Capecitabine (N=198)**	**Capecitabine (N=201)**
Number of Events	82	102	121	126
Median TTP, weeks	27.1	18.6	23.9	18.3
HR [95% CI]	0.57 [043, 0.77]		0.72 [0.56, 0.92]	
p-value	0.00013		0.00762	
RR%	23.7	13.9	31.8	17.4
p-value	0.017		0.002	

1. Hazard ratio of <1 indicates a lower risk with lapatinib + capecitabine compared to capecitabine.
2. Stratified two-sided log-rank test stratifying for stage of disease and site of disease at screening.
Data source: Study EGF 100151 report.

Reviewer: The TTP analyses by IRC and investigator supported interim analysis indicating that there is a TTP improvement for the lapatinib combination arm. However, the differences of IRC and investigator assessment were noted again.

Using same approach as for interim analysis, the difference in assessment of progression and response by IRC and investigator were analyzed. Base on the applicant's case by case comparison and the review of electronic ICR assessments (CRF, measurements and scans) by this reviewer; the major difference and reason are outlined in the tables below.

Table 14: The difference between IRC and investigator TTP assessment of Study EGF100151 at update (ITT)

	Lapatinib+ capecitabine N=198	Capecitabine N=201	Total N=399
Total Progression by IRC	**82**	**102**	**184**
Complete agreement with INV	41 (50)	59 (58)	100 (54)
PD later by INV	16 (20)	15 (15)	31 (17)
PD earlier by INV	11 (13)	15 (15)	26 (14)
Censored by INV	14 (17)[1]	13 (13)	27 (15)
Total Censored by IRC	**116**	**99**	**215**
Complete agreement with INV	55 (47)	56 (57)[2]	111 (52)
Censored later by INV	6 (5)	5 (5)	11 (5)
Censored earlier by INV	2 (2)	1 (1)	3 (1)
PD by INV	53 (46)	37 (37)	90 (42)

Data source: Study EGF 100151 report.
1. Includes two subjects who died from causes other than breast cancer.
2. Includes five subjects who died from causes other than breast cancer.

Table 15: The major reasons for difference between IRC and investigator TTP assessment of Study EGF100151 at update (ITT)

Reasons	Lapatinib+ capecitabine N=198	Capecitabine N=201	Total N=399
Total PD Events Assessed Different for TTP Analysis	**92[1]**	**80**	**172**
Interpretation of data only	47	40	87
Different selection of organ/lesions only	12	13	25
Both interpretation and selection	26	20	46
Missing data	7	7	14

1. Excludes 2 subjects who were assigned a PD event by IRC earlier than death due to competing risk by investigator.
Data source: Study EGF 100151 report.

Reviewer: As discussed with imaging consultants, the differences could be the variability in assessment (92%) and were balanced across all categories between treatment arms. Only 14 of 172 cases of disagreements (8%) were due to non-objective progression assessed by investigator or lack of radiological films available to the IRC. Existing experience on any scientific measurement involving human interpretation indicated that differences in the reviewers' observations led to differences in results, especially for the difference in selection of baseline lesions for RECIST by investigator and central reviewers. The review team formally consulted imaging team, and the imaging consultants completely agree with this reviewer's assessment. However, in this reviewer's exploratory analyses (section 6.1.4.2.2), the differences were primarily due to data not available for the independent assessment (i.e., missing data), which resulted in that the TTP improvement by independent assessment cannot be accurately characterized.

While summarizing all TTP analyses at two cut off times and by both assessment, this reviewer noticed that the median TTP of capecitabine arm were similar, whereas the median TTP of lapatinib combination arm varies, especially the TTP median TTP by IRC at interim analysis. These results indicated that although all analyses demonstrated a TTP improvement, the magnitude of this improvement varied, ranging from 5.6 to 17.6 weeks (table below).

Table 16: Summary of TTP analyses (ITT, Nov 15 2005 and Apr 3 2006 cut-off)

TTP	Nov 15 2005 cut-off N = 324				Apr 3 2006 cut-off N = 399			
	IND		INV		IND		INV	
	LC	C	LC	C	LC	C	LC	C
# Events (%)	49 (30%)	72 (45%)	59 (36%)	74 (46%)	82 (41%)	102 (51%)	121 (61%)	126 (63%)
Median TTP, weeks*	36.7	19.1	25.9	18.9	27.1	18.6	23.9	18.3
Improvement in median TTP, weeks	17.6		7		8.5		5.6	
HR [95% CI]*	0.48 [0.33, 0.70]		0.59 [0.42, 0.84]		0.57 [0.43, 0.77]		0.72 [0.56, 0.92]	
p-value*	0.00008		0.00219		0.00013		0.00762	

TTP = Time to Tumor Progression, IND = Independent Reviewer Analysis, INV = Investigators Analysis, LC = Lapatinib + Capecitabine, C = Capecitabine.
* Base on the analyses of statistical reviewer, Dr. Ko.
Source: Study EGF 100151 report applicant analyses verified by FDA.

Reviewer: At the clinical update, the magnitude of the TTP improvement became smaller and the hazard ratio became larger, which indicates differences in data availability for tumor assessment for independent review and investigator at the time of interim analysis and the clinical update. In addition, the median TTP in the lapatinib + capecitabine group was 27.1 weeks compared to 18.6 weeks on the capecitabine group by IRC assessment. This implies a 9 weeks improvement as compared to 17 weeks improvement at the earlier interim analysis by IRC assessment (Nov 15 2005 cut-off). On the other hand, the TTP improvement by the investigator analyses at both cut-off times were relatively similar, 7 week versus 6 weeks. With the confidence that all the tumor evaluation data that available and assessed by the independent review were reliable, further exploration of adequacy and validity of the TTP analyses and TTP event assessments were underway (described in next section and in section 10.1.1.3.2).

6.5.3 Exploratory Analyses for TTP in ITT Population

In order to characterize the magnitude of TTP improvement in study EGF 100151, this reviewer conducted multiple exploratory analyses after previously described assessment of IRC review quality. The exploratory analyses are primarily focused on the Completeness of TTP data that available for IRC and the worst-case scenario, as described in following sections and detailed in section 10.1.1.3.

6.5.3.1 Worst Case Scenario

a) Due to the discordance between TTP between the Independent Review and the Investigators at the interim analysis (Nov 15 2005), an exploratory analysis for TTP was performed based on the worst-case scenario for lapatinib to evaluate if the discordance could affect the overall improvement on the lapatinib combination arm. For IRC and investigator assessment agreed events or censoring cases, the later event or censoring dates by the independent review committee assessment or

investigator assessment, which ever comes later, were used if these were on the capecitabine arm. The earlier event or censoring date was chosen if it was on the lapatinib alone arm. Again, the lapatinib combination arm demonstrated an improved TTP. Please see table below and detailed in section 10.1.1.3.

Table 17: Worst-case scenario TTP analysis (ITT, Nov 15 2005 and Apr 3 2006 cut-offs)

	Lapatinib + Capecitabine (N=163)	Capecitabine (N=161)	Lapatinib + Capecitabine (N=198)	Capecitabine (N=201)
Number of Events	49 (30)	72 (45)	82 (41)	102 (51)
Median TTP, weeks	36.3	19.7	26.7	19.7
p-value*	0.00302		0.01528	

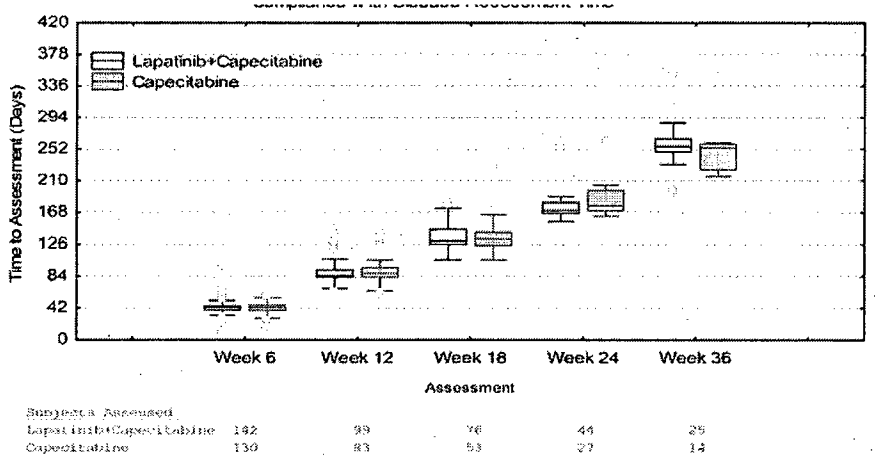
Source: Study EGF 100151 data set, result was verified by statistical reviewer, Dr. Ko.
*Log Rank P value: 0.0051 (using JMP software)

b) The statistical reviewer, Dr. Ko, further conducted a revised TTP, analyses of both cut-offs, interim analysis and clinical up date. The earlier date of TTP event and censoring by either independent review committee (IRC) assessment or investigator assessment, which ever comes first, were chosen for both arms. The revised TTP analyses indicated a 20 weeks improvement at interim analysis and a 14 weeks improvement at clinical update for the median TTP. The revised TTP appear to be better and may be more précised than IRC TTP. One explanation is that events are better distributed near the median TTP in the revised TTP analyses and TTP analysis by investigator's assessment at the clinical update (See section 10.1.1.3 for details). The distribution of events may affect the accuracy in measuring the magnitude of efficacy improvement.

6.5.3.2 Tumor assessment

The applicant has summarized the distribution of investigators' tumor assessments as per Nov 15 2005 cut-off for all subjects randomized to study EGF 100151 from the time of randomization to the time of last tumor assessment, as shown below.

Figure 6: Applicant's analysis on tumor assessment time (Nov 15 2005 cut-off)



Note: The boxes in the plot above represent medians, quartiles, and outliers beyond the inter-quartile range.

The missing tumor assessment by the investigator during the interval from the date of randomization to the date of last assessment were minimal for Nov 15 2005 cut-off, as shown below.

Table 18: Applicant's summary of missed tumor assessments for INV tumor assessments (Nov 15 2005 cut-off, amended at Ape 3 2006*)

Number of missing evaluation	L+C N= 163 (%)	C N=161 (%)	Total N = 324 (%)
No missing tumor assessment	146 (90)	150 (93)	296 (91)
Missing INV tumor assessment (≥1)	9 (5)	3 (2)	12 (4)
No data submitted to IND tumor evaluation	8 (5)	8 (5)	16 (5)
Total INV disease progression events	59	74	133
Complete INV Evaluations for Subjects with Events	57 (97)	73 (99)	130 (98)
Missing INV Evaluations for Subjects with Events	2 (3)	1 (1)	3 (2)

IND = Independent Reviewer Analysis, INV = Investigators Analysis, LC = Lapatinib + Capecitabine, C = Capecitabine.
*The data set used is amended at Apr 3 2006 cut-off.
Source: Study EGF 100151 report.

Base on the data sets provided in this NDA, the review identified number of subjects whose information was absent or insufficient for adequate tumor assessment, such as, missing any tumor assessment, baseline only, no baseline, fragment or unmatched tumor assessment data. The result is summarized as below. At interim analysis, there were 71/324 (22%) subjects without complete information for independent review. Fifty-eight (18%) subjects were censored, of them 38 (12%) were randomized less then 6 weeks. At the time of clinical update, 52 (13%) subjects with missing data for tumor evaluation. Among them, 39 (10%) subject do not have any information on independent review record, and 13 subjects (3%) with insufficient data for tumor assessment by the independent review.

Table 19: Reviewer's analyses of missed assessments for IRC tumor assessments (Nov 15 2005 and Apr 3 2006 cut-off)

Number of missing evaluation	**Nov 15 2005**			**Apr 3 2006**		
	L+C N= 163 (%)	**C N=161 (%)**	**Total N = 324 (%)**	**L+C N= 198 (%)**	**C N= 201 (%)**	**Total N = 399 (%)**
At least 1 tumor assessment beside BL	**129 (79)**	**124 (77)**	**253 (78)**	**178 (90)**	**169 (84)**	**347 (87)**
No BL or no TA during the study	**34 (21)**	**37 (23)**	**71 (22)**	**20 (10)**	**32 (16)**	**52 (13)**
Total censored without TA except BL	**32 (20)**	**26 (16)**	**58 (18)**	**16 (8)**	**20 (10)**	**36 (9)**
Censored at randomization	**32 (20)**	**26(16)**	**58 (18)**	**12(6)**	**19(9)**	**30 (7)**
Censored, Randomization < 6 weeks	*22 (13)*	*16 (10)*	*38 (12)*	*10 (5)*	*15(7)*	*25 (6)*
Censored, Randomization > 6 weeks	*10 (6)*	*10 (7)*	*20 (6)*	*2 (1)*	*4 (2)*	*5 (1)*
Censored at last TA	**0**	**0**	**0**	**4 (2)**	**1 (1)**	**5 (1)**
PD or death without TA	**2 (1)**	**7 (4)**	**9 (3)**	**4 (2)**	**8 (4)**	**12 (3)**
Other death without TA	**0**	**4(3)**	**4 (1)**	**0**	**4 (2)**	**4 (1)**

IND = Independent Reviewer Analysis, INV = Investigators Analysis, LC = Lapatinib + Capecitabine, C = Capecitabine, TA = tumor assessment, BL = baseline.
Source: Study EGF 100151 data sets.

Reviewer: Compared to Nov 15 2005 cut-off, fewer subjects with missing data in tumor assessment and fewer censoring events at the Apr 3 2006 cut-off for the independent review:

For events, 22% - 79/324 patients with no or inadequate tumor assessment at disease progression or death without tumor assessment at Nov 15 2005, vs. 13% - 57/399 patient with no or inadequate tumor assessment at disease progression or death without tumor assessment at Apr 3 2006;

Censoring, 18% - 58/324 patients censored at Nov 15 2005, vs. 9% - 36/399 patients censored at Apr 3 2006;

Of the 13% subjects with insufficient data for independent tumor assessment, 10% had completely no data available and 3% with incomplete data collection (missing baseline or no sufficient tumor evaluation that did not include disease sites).

In Conclusion, the missing data is mainly because some of the tumor evaluation data obtained and assessment by the investigator were not available for the independent reviewer to assess, especially at the interim analysis. However, the percentage of the missing data cases may not completely satisfy the degree of differences of median TTP at each cut-off time and by each assessment. This reviewer explored other type of missing data as described below.

6.5.3.3 Interval from censored last follow up date to cut-off date

Due to the discordance between the independent and investigator assessment, the review conducted exploratory analysis to compare number of patients censored and the time intervals between the cut-off date and censoring date. Subjects with an event, including progression of disease, breast cancer death and other death, were excluded. With a few minor discordances, almost all subjects censored date were documented last tumor assessment date.

Table 20: The difference of censor on last follow up date between the independent review and investigator assessment (ITT)

Interval from censored last event free follow up date to cut off date	Nov 15 2005 cut-off N = 324				Apr 3 2006 cut-off N = 399			
	LC (N= 163)		C (N=161)		LC (N=198)		C (N=201)	
	IND	INV	IND	INV	IND	INV	IND	INV
Censored (N)	114	104	85	87	116	77	99	75
Mean (weeks)	16	10	17	14	25	16	27	21
Sts Dev (± weeks)	17	13	17	16	24	21	23	25
Median (weeks)	8	6	10	10	17	5	26	6
Range (weeks)	0-63	0-58	0-68	0-71	0-83	0-78	0-88	0-90
> 14 weeks (N)	42	15	32	19	61	21	62	31

IND = Independent Reviewer Analysis, INV = Investigators Analysis, LC = Lapatinib + Capecitabine, C = Capecitabine.
Source: Study EGF 100151 data sets.

Reviewer: The protocol pre-specified follow up interval is every 6 weeks up to 24 weeks and then every 12 weeks. Therefore, the mean interval from last follow up day to cut-off day for patient without an event should be about 12 weeks or less if, the tumor assessments were all done as scheduled. However, most of the mean were larger than 12 weeks, and the IRC means were larger than that of investigator's. In addition, the means of either IND or INV were larger at the clinical update, suggesting less follow up assessment after the cut –off for interim analysis (Nov 15 2005).

The number of subjects whose censoring date is more than 14 weeks to the cut-off date were 31% for independent review (31% for each arm) versus 13% for investigator (11% for the lapatinib and capecitabine combination arm, and 15% for the capecitabine group).

The last tumor assessment as censor date for those subjects who have not reached the event at the time of the analysis, factoring with the investigator calling events earlier than the independent reviewer, had created a substantial increase in mean time of censor for last date of known contact to the 1st interim analysis of TTP by independent review assessment.

The division had been recommending with independent review on tumor response assessment, a qualitative endpoint. However, using independent review for a time to event endpoint, such as TTP, may be compromised by the missing data because the analysis is based on an endpoint, of which, a quantitative nature component is based qualitative assessment. The experience of study EGF 100151 indicated that if the investigator determined a subject with disease progression but independent reviewer disagree, no further data (radiological scans or medical photographs) were available for independent reviewer to continue assess TTP event, because the subject had taken off study as per investigator's assessment and therefore, no further objective tumor evaluation/assessment obtained. As described in section 10.1.1.3, this reviewer selected 15 cases for detailed cross reference between the datasets and CRF. This reviewer's focus was on the missing tumor assessment data. A gap exists between the investigator declared disease progression date and the independent reviewer's event (disease progression or breast cancer death) or censoring date. The gap of missing data that preventing the independent review committee to perform objective tumor assessment ranged from 27 to 172 days.

In addition, the protocol allow investigator to determine disease progression based on the symptoms without radiographic evidence available at the time of decision. This may have increased margin of this problems (3/15 cases, 20%).

Of 15 patients on this list, 6 did not received any post study treatment, 9 had no follow up (5 died $<$ 90 days and 4 died $\geq$ 90 days), suggesting insufficient post study follow up, which was prespecified in the protocol. In addition, the mismatch of independent tumor assessment date and CRF documented CT scan dates indicated data entry errors presence.

The clinical team then requested the applicant to submit CRFs of all TTP events to review. The result of the review were consistent with the 15 cases review.

Reviewer's conclusion on primary analysis of TTP: The TTP analysis at clinical update had 90% (347/399) patients' data available and 87% adequate tumor evaluation for independent review committee to assess, whereas at the time of interim analysis there were only 78% (253/324) patients' data available for independent review committee to assess. Furthermore, if the investigator determined a subject with disease progression, the subject will be off study and no further data will be able to collect for objective tumor assessment, regardless of independent reviewer's decision. Then with the composite TTP endpoint (objective disease progression and breast cancer death) and lack of further information, the independent reviewer will either censor the patient as no event, or call the TTP event at whenever the death occurs, this may lead to over estimate treatment effect for both arms assuming the errors are balanced distributed. The reviewer feels that the validity of using the independent review to characterize a time to event endpoint, such as TTP, must be carefully examined, as has occurred in this NDA review. More importantly, the magnitude of the TTP improvement of the lapatinib combination arm cannot be accurately characterized utilizing the available data from study EGF100151, especially by the interim analysis. Because of these concerns, the TTP analyses by both independent and investigator assessments at the time of clinical update would be the best estimate for the magnitude of the TTP improvement.

6.5.4 Secondary Endpoint: Overall Survival (OS)

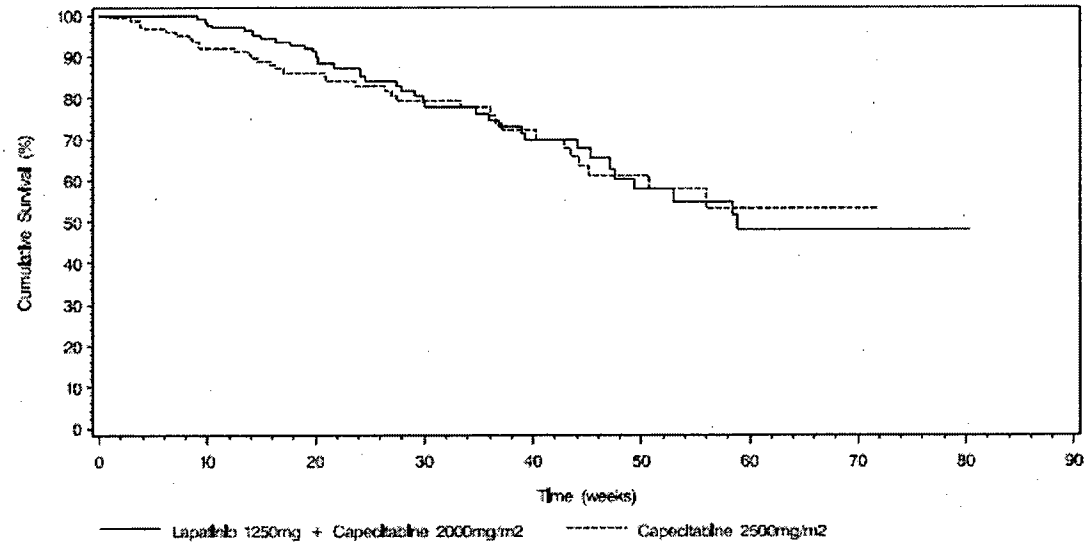
By the clinical cut-off date (Nov 15 2005) for the TTP interim analysis, 71 (22%) deaths had occurred in ITT population (22% in both the lapatinib + capecitabine combination arm and the capecitabine arm, Table and Figure below). The major reason for death (92%) in both treatment groups was disease progression (34/36 vs. 31/35 subjects, respectively). Seventy-three percent of ITT population were still being followed for survival and censored for these analyses (74% in the combination arm and 71% in the capecitabine arm. Five percent of the ITT population were no longer being following for survival but were alive at last follow-up (4% in the combination arm and 7% in the capecitabine arm).

Table 21: Study EGF100151 overall survival interim analysis (ITT, Nov 15, cut-off)

	Lapatinib + Capecitabine N=163	Capecitabine N=161	Total N = 324
Subject deaths, n (%)			
Died	36 (22)	35 (22)	71 (22)
Censored, follow-up ended	6 (4)	12 (7)	18 (5)
Censored, follow-up ongoing	121 (74)	114 (71)	235 (73)
Primary cause of death			
Progression of cancer	34 (21)	31 (19)	65 (20)
SAE	1 (<1)	3 (2)	4 (1)
Other	1 (<1)	1 (<1)	2 (<1)
Kaplan-Meier estimate of Overall Survival, weeks			
1st Quartile, [95% CI]	35.9 [28.0, 47.1]	36.6 [26.4, 45.1]	NA
Median, [95% CI]	58.9 [47.6, x]	NA [45.1, x]	NA
Hazard ratio			
Estimate, [95% CI]	0.92 [0.58,1.46]		NA
Log-rank p-value	0.717		NA

Data source: Study EGF 100151 report
NA= not applicable; x= insufficient data to estimate confidence limit.

Figure 7: Study EGF100151 overall survival Kaplan-Meier estimation at interim analysis (ITT, Nov 15, cut-off)



Reviewer: The survival data were not mature and only 22% deaths had occurred by November 15 2005. The rates of breast cancer death were similar between the two arms. The Hazard Ratio was close to 1.

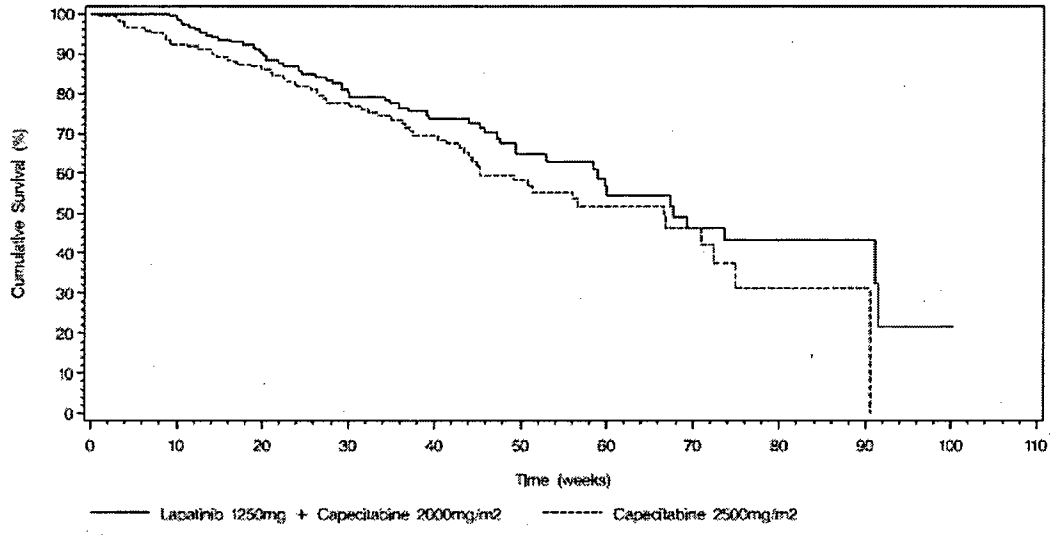
By April 3, 2006, 119 (30%) patients died out of 399 randomized subjects (ITT) (28% in the combination arm and 32% in the capecitabine arm, Table and Figure below). The principal reason for death (28%) in both treatment groups was disease progression (27% versus 29%, respectively). At the time of the analysis, 61% patients were still being followed for survival and censored for this analysis (65% in the combination arm and 58% in the capecitabine arm). Nine percent were lost to follow up, but were alive when their follow-up ended (8% in the combination arm and 10% in the capecitabine arm).

Table 22: Study EGF100151 overall survival analysis update (ITT, April 3, 2006 cut-off)

	Lapatinib + Capecitabine N=198	Capecitabine N=201	Total N = 399	Difference in KM estimate in weeks
Subject deaths, n (%)				
Died	55 (28)	64 (32)	119 (30)	
Censored, follow-up ended	15 (8)	20 (10)	35 (9)	
Censored, follow-up ongoing	128 (65)	117 (58)	245 (61)	
Primary cause of death				
Progression of cancer	53 (27)	59 (29)	112 (28)	
SAE	1 (<1)	4 (2)	5 (1)	
Other	1 (<1)	1 (<1)	2 (<1)	
Kaplan-Meier estimate of Overall Survival, weeks				
1st Quartile, [95% CI]	39.0 [29.1,49.3]	33.4 [25.6,42.9]	NA	5.6
Median, [95% CI]	67.7 [58.9,91.6]	66.6 [49.1,75.0]	NA	1.1
3rd Quartile, [95% CI]	91.6 [91.1, x]	90.6 [72.4, 90.6]	NA	1
Hazard ratio				
Estimate, [95% CI]	0.78 [0.55,1.12]		NA	
Log-rank two-sided p-value	0.177		NA	

Data source: Study EGF 100151 report
NA= not applicable; x= insufficient data to estimate confidence limit.

Figure 8: Study EGF100151 overall survival Kaplan-Meier estimation update (ITT, April 3, 2006 cut-off)



Data source: Study EGF 100151 report

Reviewer: With 30% deaths, these updated survival data were still immature. The breast cancer deaths rate was only 4% less in the combination arm (28% vs. 32%). However, the Kaplan-Meier curves of the two arms separated clearly. The hazard ratio for OS on the lapatinib combination arm relative to capecitabine was 0.78, less than the hazard ratio of 0.92 for OS by Nov 15, 2005. An early trend towards an improved survival can be considered.

Even though the control arm has crossed over after the Apr 3 2006 cut-off, it would be worthwhile to continue follow up for survival and conduct survival analyses at 75% events, as the protocol prespecified OS analyses were planned at 30%, 60% and 80% with a sample size of 528 patients.

6.5.5 Secondary Endpoint: Progression Free Survival (PFS)

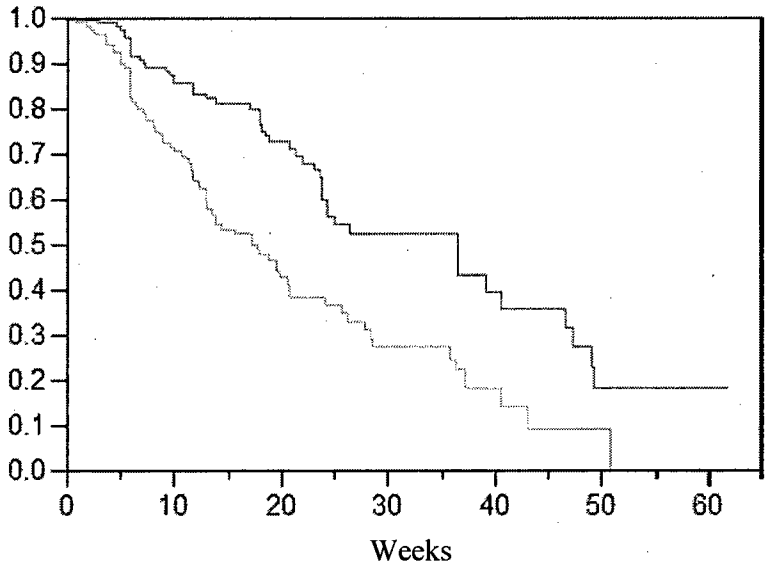
Based on IRC assessment of tumor response, the median PFS at interim analysis was 36.7 weeks on the combination arm and 17.9 week on the control arm with a hazard ratio of 0.47 (p = 0.000023, Table below).

Table 23: Study EGF 100151 PFS analysis by IRC assessment (ITT, Nov 15, 2006 cut-off)

	Lapatinib + Capecitabine N=163	Capecitabine N=161
Subject status, n (%)		
Progressed or died at or prior to 6 months	49 (30)	76 (47)
Censored, follow-up ended	9 (6)	12 (7)
Censored, follow-up ongoing	105 (64)	73 (45)
Kaplan-Meier estimate of PFS, weeks		
1st Quartile, [95% CI]	18.7 [14.1,24.1]	8.7 [6.6, 12.0]
Median, [95% CI]	36.7 [24.1, 46.9]	17.9 [13.3,21.0]
3rd Quartile, [95% CI]	49.4 [40.7, x]	36.0 [25.9,43.4]
Hazard Ratio [95% CI]	0.47 [0.33, 0.67]	
Log-rank p-value	0.000023	

Data source: Study EGF 100151 report

Figure 9: Study EGF 100151 PFS by IRC assessment (ITT, Nov 15 2005 cut-off)



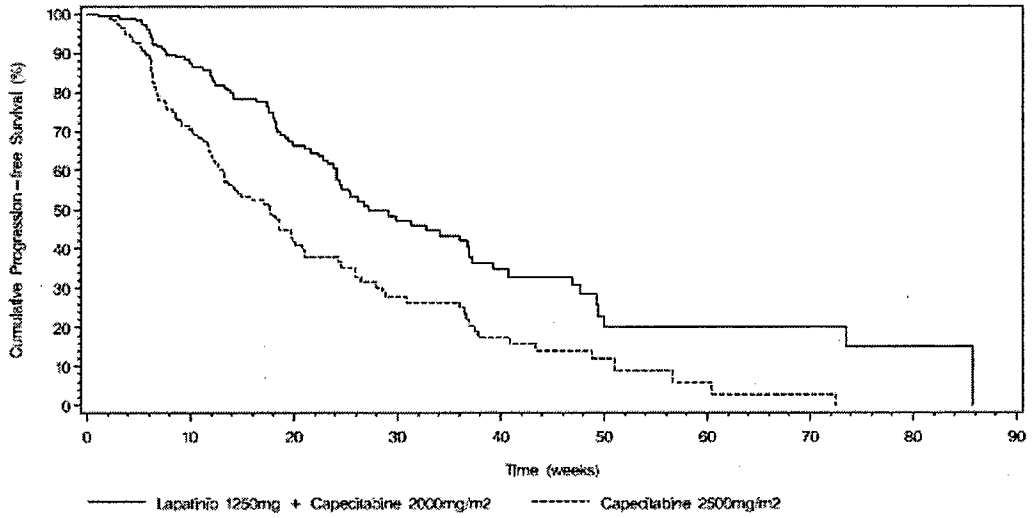
At the time of analysis update (Apr 3, 2006), the IRC assessed median time for progression-free survival (PFS) was 27.1 weeks in the combination arm and 17.6 weeks in the capecitabine arm with a hazard ratio of 0.55 (95% CI: 0.41, 0.74, two-sided p=0.000033, shown in Table and Figure below).

Table 24: Study EGF 100151 PFS analysis update (ITT, Apr 3 2006 cut-off)

	Lapatinib + Capecitabine N=198	Capecitabine N=201
Subject progression, n (%)		
Progressed or died	82 (41)	107 (53)
Censored, follow-up ended	20 (10)	23 (11)
Censored, follow-up ongoing	96 (48)	71 (35)
Kaplan-Meier estimate of PFS, weeks		
1st Quartile, [95% CI]	17.4 [13.6,19.9]	8.3 [6.6,11.4]
Median, [95% CI]	27.1 [24.1,36.9]	17.6 [13.3,20.1]
3rd Quartile, [95% CI]	49.4 [39.3,85.7]	36.4 [25.9,40.9]
Hazard ratio		
Estimate, [95% CI]	0.55 [0.41,0.74]	
Log-rank two-sided p-value	0.000033	

Data source: Study EGF 100151 report

Figure 10: Kaplan-Meier Estimates of Progression-free Survival (ITT, Apr 3 2006 Cut-off)



Reviewer: The PFS result is similar to that of TTP, since the difference between the two was 5 non-breast cancer death as per Apr 3 2006 cut-off, which were very small (< 2%).

6.5.6 Secondary Endpoint: Response Rate (RR)

At the time of interim analysis, the response rate (complete or partial response) assessed by IRC was 22% in the combination arm versus 14% in the capecitabine arm. The odds ratio was 1.7 (95% CI: 0.9, 3.2, p-value = 0.091, as shown in Table below).

Table 25: Study EGF 100151 Response Rate by IRC assessment (ITT, Nov 15, 2006 cut-off)

Response, n (%)	Lapatinib+ Capecitabine N=163	Capecitabine N=161
Complete response (CR)	1 (<1)	0
Partial response (PR)	35 (21)	23 (14)
Stable disease (SD)	57 (35)	48 (30)
Progressive disease (PD)	16 (10)	33 (20)
Unknown	54 (33)	57 (35)
Response rate (CR or PR)[1], % [95% CI]	**22.1 [16.0, 29.2]**	**14.3 [9.3, 20.7]**
Difference in response rate (CR or PR), % [95% CI]	**7.8 [-2.1, 18.4]**	
Estimate of common odds ratio for tumor response [95% CI]	**1.7 [0.9, 3.2]**	
Exact test p-value	**0.091**	

Data source: Study EGF 100151 report
1. Subjects with unknown or missing responses were treated as non-responders.

At the time of update, the response rate (complete or partial response) by IRC assessment was 24% in the combination arm group versus 14% in the capecitabine arm. The odds ratio was 1.9 (95% CI: 1.1, 3.4, two-sided p = 0.017, as shown Table below).

Table 26: Study EGF 100151 Response Rate by IRC assessment (ITT, Apr 3, 2006 Cut-off)

Response, n (%)	Lapatinib + Capecitabine N=198	Capecitabine N=201
Complete response (CR)	1 (<1)	0
Partial response (PR)	46 (23)	28 (14)
Stable disease (SD)	75 (38)	59 (29)
Progressive disease (PD)	25 (13)	47 (23)
Unknown	51 (26)	67 (33)
Response rate (CR or PR)[1], % [95% CI]	**23.7 [18.0,30.3]**	**13.9 [9.5,19.5]**
Difference in response rate (CR or PR), % [95% CI]	**9.8 [0.8,19.3]**	
Estimate of common odds ratio for tumor response [95% CI]	**1.9 [1.1,3.4]**	
Exact test two-sided p-value	**0.017**	

Data source: Study EGF 100151 report
1. Subjects with unknown or missing responses were treated as non-responders.

Reviewer: The response rate was not statistically better for the combination arm at the time of interim analysis (n = 324). However, with increase of sample size, the response rate became statistically better for the combination arm (n = 399). There were 11 more PR in combination arm and 5 more PR in control arm by the update, but no additional CRs were identified.

The data sets did not contain information of patients' baseline Her2 status, since it was on a separated work sheet that was not part of the CRF. Upon FDA request, the applicant submitted Her2 baseline status summary based on the information collected from the investigator's worksheet as Apr 3 2006 cut-off date, as shown below. Not data set provided for verification.

Table 27: Study EGF 100151 Her2 positive responders by IRC assessment (ITT, Apr 3 2006 cut-off)

Her 2 status \ Treatment arms	Randomized Treatment			Actual Treatment Received		
	LC N=198 (%)	C N=201 (%)	Total N = 399 (%)	LC N=198 (%)	C N=191 (%)	Total N = 389 (%)
Total PR	23 (12)	16 (8)	39 (10)	26 (13)	13 (7)	39 (10)
Her 2 Positive	23 (12)	16 (8)	39 (10)	26 (13)	13 (7)	39 (10)
IHC 3+	21 (11)	13 (6)	34 (9)	24 (12)	10 (5)	34 (9)
IHC2+ FISH	2 (1)	3 (1)	5 (1)	2 (1)	3 (2)	5 (1)

Source: additional data submitted by the applicant per reviewers' request.
LC = Lapatinib + capecitabine, C = capecitabine

6.5.7 Duration of the response

For subjects who had CR or PR, the duration of response was assessed by IRC at the time of interim analysis (Nov 15, 2005) and the time of update (Apr 3, 2006), as shown in table below.

Table 28: Study EGF 100151 response duration by IRC (ITT, Nov 15, 2005 and Apr 3, 2006 cut-off)

Progression and death, n (%)	Nov 15, 2005 cut-off		Apr 3, 2006 cut-off	
	Lapatinib+ Capecitabine N=163	Capecitabine N=161	Lapatinib+ Capecitabine N = 198	Capecitabine N = 201
CR or PR, N	36	23	47	29
Progressed or died due to breast cancer	11 (31)	8 (35)	19 (40)	12 (43)
Died due to cause other than breast cancer	0	0	0	0
Censored, follow-up ended	1 (3)	2 (9)	6 (13)	3 (11)
Censored, follow-up ongoing	24 (67)	13 (57)	22 (47)	13 (46)
Cumulative incidence estimate of duration of response, weeks				
1st Quartile	27.3	19.1	21.0	24.3
Median	35.1	30.7	32.1	30.6
3rd Quartile	NA	32.3	NA	32.3

Data source: Study EGF 100151 report
NA = not available

Reviewer: The response duration demonstrated a mild improvement in the combination arm at the time of interim analysis, but this improvement did not appear to sustain itself by the time of update.

6.6 Efficacy Summary of Other Supportive Studies

As reported by the applicant, the response rate of single arm studies of lapatinib alone in refractory breast cancer patients are summarized as below.

Table 29: Summary of independent panel and investigator evaluated response rate (ITT population) Studies EGF20008 and EGF20002

Study	EGF20008				EGF20002 N=78	
	Cohort A (N=140)		Cohort B (N=89)			
Assessment	IND	INV	IND	INV	IND	INV
Complete response (CR), n (%)	0	3 (2)	0	0	0	1 (1)
Partial response (PR), n (%)	2 (1)	3 (2)	0	0	4 (5)	5 (6)
Stable disease (SD), n (%)	46 (33)	38 (27)	10 (11)	10 (11)	31 (40)	29 (37)
Progressive disease (PD), n (%)	64 (46)	85 (61)	49 (55)	76 (85)	26 (33)	40 (51)
Unknown, n (%)	28 (20)	11 (8)	30 (34)	3 (3)	17 (22)	3 (4)
Response rate, % [95% CI]	1.4 [0.2, 5.1]	4.3 [1.6, 9.1]	0 [0.0, 4.1]	0 [0.0, 4.1]	5.1 [1.4, 12.6]	7.7 [2.9, 16.0]

Source: EGF 20002 and 20008 study reports.

6.7 Clinical Microbiology

Not applicable.

6.8 Efficacy Conclusions

EGF 100151 was a randomized, open label study in patients with ErbB2 overexpressing, advanced/metastatic breast cancer that had been previously exposed to anthracycline-, taxane- and trastuzumab-containing regimens. The patients were treated with capecitabine, with or without lapatinib. At the prespecified interim analysis at time of 30% events occurrence (cut-off date of November 15, 2005), superiority on the lapatinib combination arm was observed based on crossing of the O'Brien-Fleming boundary. IDMC advice resulted in the closure of the study to further enrollment on April 3, 2006, with 399 patients enrolled of planned 528 patients. Patients on the capecitabine alone arm were allowed to crossover to the lapatinib combination arm. The primary analyses were based on central, blinded, independent reviewers' analyses.

1) Time to Tumor Progression (TTP):

Time to Tumor Progression defined by time from randomization to the earliest time of tumor progression or death was the primary endpoint. At the interim analysis the median TTP improved by 17.6 weeks on the lapatinib combination arm (19 weeks: capecitabine arm; 37 weeks: lapatinib combination arm; HR: 0.49 [0.34, 0.71]) based on the independent reviewer's analysis.

This improvement decreased to 8.5 weeks by the updated analysis with cut-off date of April 3, 2006. The investigator analysis also demonstrated improvement in TTP at the initial and updated cut-off dates, but remained small at 7 and 5.6 weeks, respectively.

Table 30: Study EGF100151 TTP analyses summary (ITT)

TTP	Nov 15 2005 cut-off N = 324				Apr 3 2006 cut-off N = 399			
	IND		INV		IND		INV	
	LC	C	LC	C	LC	C	LC	C
Total Events (%)	49 (30%)	72 (45%)	59 (36%)	74 (46%)	82 (41%)	102 (51%)	121 (61%)	126 (63%)
Median TTP, weeks	36.7	19.1	25.9	18.9	27.1	18.6	23.9	18.3
Improvement in median TTP, weeks	17.6		7		8.5		5.6	
HR [95% CI]	0.48 [0.33, 0.70]		0.59 [0.42, 0.84]		0.57 [0.43, 0.77]		0.72 [0.56, 0.92]	
p-value	0.00008		0.00219		0.00013		0.00762	

TTP = Time to Tumor Progression, IND = Independent Reviewer Analysis, INV = Investigators Analysis, LC = Lapatinib + Capecitabine, C = Capecitabine,
Source: Study EGF 100151 report applicant analyses verified by FDA.

The TTP analysis at clinical update had 90% (347/399) patients' data available and 87% adequate tumor evaluation for independent review committee to assess, whereas at the time of interim analysis there were only 78% (253/324) patients' data available for independent review committee

to assess. Furthermore, if the investigator determined a subject with disease progression, the subject will be off study and no further data were able to collect for objective tumor assessment, regardless the opinion of the independent reviewer. With the composite TTP endpoint (objective disease progression and breast cancer death) and lack of further information, the independent reviewer will either censor the patient as no event, or call the TTP event at whenever the death occurs, this may lead to over estimate treatment effect for both arms assuming the errors are balanced distributed. Based on the study EGF 100151 primary analysis data review experience, the reviewer feels that the validity of using independent review to adjudicate a time to event endpoint, such as TTP, with missing data in 22% cases is questionable. More importantly, the magnitude of the TTP improvement of lapatinib combination arm cannot be accurately characterized utilizing available data from study EGF100151, especial by the interim analysis. Because of the above concerns, TTP improvement is best presented through analyses of both independent and investigator assessments at the time of clinical update.

2) Overall Survival (OS):

The data on overall survival was immature by time of both the interim analysis and the clinical update (22% deaths by November15th, 2006 and 30% by April 3 2006). The overall survival analysis indicated no statistical difference between the two arms. Although the updated survival analysis did not result any statistical significance either, the Kaplan-Meier curves for the two treatment arms separated wider suggesting early trend in a survival advantage for the combination arm.

Table 31: Study EGF100151 OS analyses summary (ITT)

OS	Nov 15 2005 cut-off N = 324		Apr 3 2006 cut-off N = 399	
	LC	C	LC	C
Median OS, weeks	58.9	NA	67.7	66.6
HR [95% CI]	0.92 [0.58, 1.46]		0.78 [0.55, 1.12]	
p-value	0.717		0.177	

LC = Lapatinib + Capecitabine, C = Capecitabine,
Source: Study EGF 100151 report applicant analyses verified by FDA.

3) Progression Free Survival (PFS):

PFS at the interim analysis and at the clinical update was almost identical to the TTP analysis, because the non-breast cancer death rate was less than 2%. The difference in TTP and PFS definitions in this study was based on attribution of causality of death only.

Table 32: Study EGF100151 PFS analyses summary (ITT, IRC assessment)

PFS	Nov 15 2005 cut-off		Apr 3 2006 cut-off	
	LC	C	LC	C
Median PFS, weeks	36.7	17.9	27.1	17.6
HR [95% CI]	0.47 [0.33, 0.67]		0.55 [0.41, 0.74]	
p-value	0.00023		0.000033	

LC = Lapatinib + Capecitabine, C = Capecitabine,
Source: Study EGF 100151 report applicant analyses verified by FDA.

4) Response Rates and Response Duration

There was an improvement in response rate at the interim analysis and the update. Although p value was less than 0.05, statistical significance cannot be ascertained due to multiplicity. Only one CR (combination arm) observed by the independent reviewer.

Median response durations improvements were small between the two treatment arms. This implies a disease stabilization affect from the use of lapatinib.

Table 33: Study EGF100151 RR and response duration analyses summary (ITT, IRC assessment)

Response	Nov 15 2005 cut-off		Apr 3 2006 cut-off	
	LC	C	LC	C
Median Response Duration	35.1	30.7	32.1	30.6
RR%	22.1	14.3	23.7	13.9

LC = Lapatinib + Capecitabine, C = Capecitabine,
Source: Study EGF 100151 report applicant analyses verified by FDA.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

As applicant indicated, the safety profile of lapatinib as combination therapy with other treatments and as monotherapy has been evaluated in 3,147 subjects with cancer and healthy subjects in 52 completed or ongoing clinical studies sponsored by GSK. The table below listed all subjects treated in completed lapatinib studies that sponsored by GSK.

Table 34: Subjects treated in completed lapatinib studies sponsored by GSK

	Lapatinib / capecitabine combination	Lapatinib monotherapy	Capecitabine monotherapy	Lapatinib in combination with other treatment
Refractory Metastatic Breasts Cancer	164[1]	307[2]	152[3]	
Other Solid Tumors	45[4]			
Metastatic breast cancer				
Other cancer/Solid tumors				
Healthy subjects		235		24
Subtotal other studies		555		78
Total	209	862	152	78

Source: EGF 20002 and 20008 study reports.
1. Study EGF100151, 164 received study drug; 163 were enrolled and randomized.
2. Study EGF 2002 and 2008
3. 152 received study drug; 161 were enrolled and randomized.
4. Includes 7 subjects with breast cancer in the Phase 1 Study EGF10005.
5. 54 received study drug; 208 enrolled and randomized.
6. Study EGF10023.

The safety review is focused on the safety data of study EGF 100151 of lapatinib in combination with capecitabine, which was analyzed by applicant and verified by reviewer, for both the interim analysis (clinical cut-off date of 15 November 2005) and update (cut-off date of Apr 3, 2006). Safety evaluations included AEs, clinical laboratory tests, vital signs, ECOG Performance Status, electrocardiograms, and echocardiograms/MUGA scans. The safety population (SP) was based on the actual treatment received. As motioned before, 7 subjects were randomized to lapatinib + capecitabine but received capecitabine and 9 subjects were randomized to capecitabine but received lapatinib + capecitabine (see section 10.1.1.2). The safety evaluation included all subjects who received at least one dose of study medication (SP). The safety results are summarized in table below and presented in the following sections.

Table 35: Study EGF 100151 adverse events by category (SP, Nov 15 2005 cut-off)

MedDRA Preferred Term	Lapatinib+ Capecitabine N=164, n (%)	Capecitabine N=152, n (%)
Any AE	146 (89)	138 (91)
AEs leading to treatment termination	22 (13)	13 (9)
Any SAE	40 (24)	36 (24)
Fatal SAEs	2 (1)	3 (2)

Data source: Study EGF 100151 report

Reviewer: About 90% patients had at least one adverse event and no big differences were observed in the AEs that led to discontinuations of treatment, serious adverse events and fatalities resulting from treatment.

7.1.1 Deaths

Six cases deaths (applicant identified 5 and reviewer identified an additional one) with an SEA recorded during the study EGF 100151; two were in combination arm and 3 in the capecitabine arm, detail shown in table below.

Table 36: Study EGF 100151 death related AEs regardless of relationship (SP, Nov 15 2005 cut-off)

MedDRA Preferred Term	Lapatinib+ Capecitabine N=164, n (%)	Capecitabine N=152, n (%)
Any fatal SAE	2 (1)	3 (2)
Cardiac arrest	0	1 (<1)
Cardio-respiratory arrest	1 (<1)	0
Diarrhea	0	1 (<1)[1]
Small intestinal obstruction	0	1 (<1)[1]
Vomiting	0	1 (<1)[1]
Respiratory arrest	0	1 (<1)
Lymph edema[2]	1 (<1)	0
Budd Chiari Syndrome	1 (<1)	0

Data source: Study EGF 100151 report
Note: There may be more than one event entered for each subject.
1. Subject 52653/513 had SAEs of diarrhea, small intestinal obstruction and vomiting that resulted death.
2. Subject 128 died with severe lymph edema/anasarca due to disease progression. Therefore, the cause of death should not be due to AE but due to disease progression.

Reviewer: The death related AE cases were less than 2% and were similar between the two arms. One of 5 death identified by investigators are due to disease progression (Sub#128, lymph edema). One additional death related AE was identified by the reviewer.

At the time of clinical update (Apr 3 2006), 11 subjects died with and SEA recorded during the study, four in the lapatinib + capecitabine arm and seven in the capecitabine group, as shown in table below.

Table 37: EGF 100151 death related AEs update (SP, Apr 3 2006 cut-off)

MedDRA Preferred Term	Lapatinib + Capecitabine N=198 (%)	Capecitabine N=191 (%)
Total fatal event	4 (2)	7 (4)
Disease progression[2]	1 (<1)	1 (<1)
Bone pain	0	1 (<1)
Cardiac arrest	0	1 (<1)
Cardio-respiratory arrest	1 (<1)	0
CNS metastases	1 (<1)	0
Diarrhea[1]	0	1 (<1)
Lymph edema[2]	1 (<1)	0
Budd-Chiari Syndrome	1 (<1)	0
Neutropenia	0	1 (<1)
Pulmonary embolism	0	1 (<1)
Respiratory arrest	0	1 (<1)
Small intestinal obstruction	0	1 (<1)
Thrombocytopenia	0	1 (<1)
Vomiting	0	1 (<1)

Data source: Study EGF 100151 report
Note: There may be more than one event entered for each subject.
1. Diarrhea includes incidences of diarrhea, loose stools and frequent bowel movements.
2. Subject 128 died with severe lymph edema/anasarca due to disease progression. Therefore, the cause of death should not be due to AE but due to disease progression.

Reviewer: Five cases of death related AE were observed at the interim analysis, and 6 more death that related to AEs were reported at the clinical update. Overall more fatal AEs were reported in the control arm, which may due to the higher dose of capecitabine. Three of the 11 fatal AEs in the capecitabine arm were considered to be related to the study medication by the investigator. These cases are:
- Subject 513 had SAEs of diarrhea, small intestinal obstruction and vomiting that lead to death;
- Subject 1384 had SAEs of neutropenia and thrombocytopenia that lead to death;
- Subject 25 had a SAE of pulmonary embolism that lead to death.

No subjects in the lapatinib + capecitabine arm died with a SAE that was considered to be related to the study medication by the investigator. In reviewer's opinion, the cases of cardio-respiratory arrest and Budd-Chiari syndrome observed on lapatinib combination arm are difficult to be considering as unrelated or unlikely related.

The early deaths observed during study were minimal. There were no 30 and 60 day death on the lapatinib combination arm. The 30, 60, and 100 day deaths observed at both cut-off dates are summarized as below.

Table 38: Death within 30, 60, and 100 days (SP)

Reason	Nov 15 2005 cut-off		Apr 3 2006 cut-off	
	Lapatinib + Capecitabine N = 164 (%)	Capecitabine N = 152 (%)	Lapatinib + Capecitabine N=198 (%)	Capecitabine N=191 (%)
30 days				
PD	0	1 (<1)	0	3 (2)
AE	0	4 (3)	0	4 (2)
Other	0	0	0	0
60 days				
PD	0	5 (3)	0	7 (4)
AE	0	4 (3)	0	5 (3)
Other	0	0	0	0
100 days				
PD	6 (4)	10 (7)	10 (5)	13 (7)
AE	0	4 (3)	0	5 (3)
Other	0	0	0	0

Data source: Study EGF 100151 report

Reviewer: For either cut-off date, there was no death within 60 days on the lapatinib combination arm. The deaths (4-5%) on lapatinib combination arm during the first 100 days were all due to progression of disease. The percentage of 30, 60 and 100 days deaths, either due to progression of disease (7%) or adverse event (3%), on capecitabine control arm was small.

Of the 307 subjects enrolled in Study EGF20002 and Study EGF20008, 53 (17%) died within 30 days of the last dose, all due to progression of cancer as the primary cause. As the majority of subjects were white and less than 65 years of age, no statistical comparisons could be made but the data do not appear to indicate a difference between the subgroups. The result were summarized by the applicant and verified by the reviewer, as shown below.

Table 39: Deaths within 30 Days of Last Dose – Studies EGF20002 and EGF20008

	Lapatinib 1250mg (N=34)	Lapatinib 1500mg (N=273)	Total (N=307)
Death, N (%)	4 (12%)	49 (18%)	53 (17%)
Primary cause of death			
Progression of cancer	4 (12%)	49 (18%)	53 (17%)
Serious adverse event	0	0	0
Other	0	0	0

Source: Study EGF20002 and 2008 reports.

All AEs related death observed in studies EGF 20002 and EGF 20008 were summarized by the applicant and verified by the reviewer, as shown below.

Table 40: Fatal Adverse Events - Studies EGF20002 and EGF20008

System / Preferred Term	Lapatinib 1250mg (N=34)	Lapatinib 1500mg (N=273)	Total (N=307)
ANY EVENT	0	4 (1%)	4 (1%)
Respiratory, thoracic, and mediastinal disorders			
Any Event	0	4 (1%)	4 (1%)
Respiratory failure	0	2 (<1%)	2 (<1%)
Dyspnea	0	1 (<1%)	1 (<1%)
Respiratory arrest	0	1 (<1%)	1 (<1%)
Cardiac disorders			
Any Event	0	1 (<1%)	1 (<1%)
Cardiac failure	0	1 (<1%)	1 (<1%)
Renal and urinary disorders			
Any Event	0	1 (<1%)	1 (<1%)
Renal failure	0	1 (<1%)	1 (<1%)

Source: Study EGF20002 and 2008 reports.

Reviewer: Higher death rate and AE related death observed in lapatinib 1500 mg/day regimen. The death and AE related deaths in single agent lapatinib 1250 mg/day treatment were no worse to the lapatinib 1250 mg/day in combination with capecitabine.

7.1.2 Other Serious Adverse Events

Total of 40% subjects experienced SAEs in lapatinib/capecitabine combination arm and 36% of subjects experienced SAEs in capecitabine arm. Incidence of grade 3 or 4 AEs ($\geq$ 2 subjects in combination arm) are listed by occurring frequency in the table below.

Table 41: Study EGF 100151 SAEs (≥ 2 subjects) regardless of relationship (SP, Nov 15 2005 cut-off)

MedDRA Preferred Terms	Lapatinib + Capecitabine N = 164				Capecitabine N = 152			
	G3-4	%	All	%	G3-4	%	All	%
Diarrhea	21	13	98	60	17	11	60	39
Palmar-plantar erythrodysesthesia syndrome	12	7	80	49	16	11	74	49
Hypokalemia	5	3	6	4	2	1	5	3
Dyspnea	5	3	18	11	3	2	10	7
Neutropenia	3	2	4	2	4	3	9	6
Nausea	3	2	72	44	3	2	63	41
Vomiting	3	2	43	26	3	2	36	24
Fatigue	3	2	29	18	6	4	41	27
Dehydration	3	2	7	4	2	1	7	5
Abdominal pain	2	1	16	10	2	1	25	16
Back pain	2	1	17	10	1	1	9	6
Bone pain	2	1	11	7	1	1	6	4
Lethargy	2	1	8	5	0	0	4	3
Depression	2	1	4	2	0	0	4	3
Pulmonary embolism	2	1	2	1	1	1	1	1
Rash	2	1	45	27	2	1	23	15

Data source: Study EGF 100151 report

Reviewer: The total incidence of SAEs observed in study EGF 100151 was similar between both combination and capecitabine arms. However, the dose of capecitabine was 25% higher for the control arm. The most common SAEs were diarrhea and PPE for both arms, 13% and 7% for lapatinib/capecitabine arm vs. 11% and 11% for capecitabine arm, respectively.

The SAE update analysis was conducted in SP population and based on the data from Apr 3 2006 cut-off, as shown in table below.

Table 42: EGF 100151 SAEs (≥ 2 incidences, regardless relationship) update (SP, Apr 3 2006 cut-off)

MedDRA Preferred Terms	Lapatinib + Capecitabine N = 198				Capecitabine N = 191			
	G3-4	%	All	%	G3-4	%	All	%
Diarrhea	26	13	124	63	20	10	80	42
Palmar-plantar erythrodysesthesia	24	12	102	52	26	14	100	52
Hypokalemia	6	3	10	5	2	1	6	3
Dyspnea	6	3	22	11	4	2	17	9
Dehydration	5	3	9	5	2	1	8	4
Vomiting	4	2	49	25	3	2	44	23
Fatigue	4	2	44	22	8	4	49	26
Neutropenia	3	2	7	4	6	3	14	7
Nausea	3	2	87	44	3	2	83	43
Asthenia	3	2	23	12	3	2	21	11
Rash	3	2	51	26	2	1	30	16
Abdominal pain	2	1	26	13	2	1	29	15
Back pain	2	1	22	11	1	1	11	6
Pain in extremity	2	1	23	12	1	1	14	7
Cancer pain	2	1	2	1	0	0	0	0
Depression	2	1	6	3	0	0	5	3
Pulmonary embolism	2	1	2	1	1	1	1	1

Data source: Study EGF 100151 report

Reviewer: The updated common AEs were consistent with the results at the interim analysis.

Overall, serious events were reported for 76 (25%) of subjects in the Study EGF20002 and Study EGF20008 studies (Table below). The most common serious events were diarrhea (4%) and dehydration (3%). Similar proportions of serious events were observed among subjects who were less than 65 years of age. Among subjects 65 years of age and older, the most common serious events were diarrhea, pleural effusion, respiratory failure, and dehydration (4% each). The pattern of SAEs did not appear to be notably different based on race, although limited representation of non-whites prevents firm conclusions about differences based on race.

Table 43: Serious AEs in studies EGF20002 and EGF 20008 regardless treatment relationship

System / Preferred Term	Lapatinib 1250mg N=34)	Lapatinib 1500mg (N=273)	Total (N=307)
ANY EVENT	7 (21%)	69 (25%)	76 (25%)
Gastrointestinal disorders (any event)	2 (6%)	20 (7%)	22 (7%)
Diarrhea	2 (6%)	9 (3%)	11 (4%)
Nausea	0	6 (2%)	6 (2%)
Vomiting	0	6 (2%)	6 (2%)
Abdominal pain	0	5 (2%)	5 (2%)
Abdominal pain upper	0	1 (<1%)	1 (<1%)
Ascites	0	1 (<1%)	1 (<1%)
Gastrointestinal disorder	0	1 (<1%)	1 (<1%)
Gastrointestinal perforation	0	1 (<1%)	1 (<1%)
Peptic ulcer haemorrhage	0	1 (<1%)	1 (<1%)
Rectal haemorrhage	0	1 (<1%)	1 (<1%)
Infections and infestations (any event)	1 (3%)	13 (5%)	14 (5%)
Cellulitis	0	5 (2%)	5 (2%)
Pneumonia	0	2 (<1%)	2 (<1%)
Biliary tract infection	0	1 (<1%)	1 (<1%)
Brain abscess	1 (3%)	0	1 (<1%)
Gastroenteritis	0	1 (<1%)	1 (<1%)
Infection	0	1 (<1%)	1 (<1%)
Staphylococcal sepsis	0	1 (<1%)	1 (<1%)
Urinary tract infection	0	1 (<1%)	1 (<1%)
Wound infection	0	1 (<1%)	1 (<1%)

Source: Study EGF20002 and 2008 reports.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The dropouts in studies EGF100151, EGF 2002, and EGF 2008 are listed in the tables below by drop our categories.

Table 44: Study EGF100151 subject accountability (ITT)

Study Outcome		Lapatinib + Capecitabine N=163 n (%)	Capecitabine N=161 n (%)	Total N=324 n (%)
Status	Completed treatment[1]	1 (<1)	1 (<1)	2 (<1)
	Discontinued treatment	41 (25)	46 (29)	87 (27)
	Ongoing[2]	121 (74)	114 (71)	235 (73)
Reason for Premature Discontinuation	Death	33 (20)	34 (21)	67 (21)
	Consent withdrawn	3 (2)	9 (6)	12 (4)
	Other	2 (1)[3]	3 (2)[4]	5 (2)
	Lost to follow-up	3 (2)	0	3 (<1)

Source: Study EGF100151 report.
1. As recorded on the end of study record
2. As of clinical cutoff date of 15 November 2005
3. Both subjects withdrew due to disease progression
4. One subject withdrew due to disease progression, one subject due to the development of cerebral metastases and one subject due to a mastectomy.

Table 45: Analyses on study drug discontinuation

Subject Accountability	Lapatinib 1250mg (N=34)	Lapatinib 1500mg (N=273)	All Subjects (N=307)
Investigational Treatment Termination			
All Subjects	34 / 34(100%)	262 / 273 (96%)	296 / 307 (96%)
Subjects <65 years	27 / 27(100%)	224 / 234 (96%)	251 / 261 (96%)
Subjects ≥ 65 years	7 / 7(100%)	38 / 39 (97%)	45 / 46 (98%)
Termination Reason			
Adverse Events	1 / 34 (3%)	19 / 262 (7%)	20 / 296 (7%)
Consent withdrawn	0 / 34	5 / 262 (2%)	5 / 296 (2%)
Death	0 / 34	3 / 262 (1%)	3 / 296 (1%)
Radiological Progression of Cancer	27 / 34 (79%)	178 / 262 (68%)	205 / 296 (69%)
Symptomatic Progression of Cancer	6 / 34 (18%)	53 / 262 (20%)	59 / 296 (20%)
Other	0 / 34	4 / 262 (2%)	4 / 296 (1%)

Source: Study EGF20002 and 2008 reports.

Reviewer: The most common reason for discontinuation of treatment was disease progression. In studies EGF 2002 and EGF 2008 similar drop out pattern was observed regardless of age group. There were no notable differences in discontinuations based on race; however, the limited number of non-whites limits firm conclusions based on race. Overall, 7% of subjects withdrew due to AEs.

7.1.3.2 Adverse events associated with dropouts

The AEs that lead to treatment termination are summarized in the table below.

Table 46: Study EGF 100151 AEs caused treatment termination regardless of relationship (SP, Nov 15 2005 cut-off)

MedDRA Preferred Term	Lapatinib+ Capecitabine N=164 (%)	Capecitabine N=152 (%)
Any AE leading to discontinuation	22 (13)	13 (9)
Diarrhea	8 (5)	4 (3)
PPE	4 (2)	3 (2)
Nausea	3 (2)	2 (1)
Vomiting	2 (1)	2 (1)
Rash	3 (2)	0
Mucosal inflammation	1 (<1)	1 (<1)
Pulmonary embolism	1 (<1)	1 (<1)

Data source: Study EGF 100151 report

Table 47: Study EGF 100151 AEs caused treatment termination regardless of relationship (SP, Apr 3 2006 cut-off)

MedDRA Preferred Term	Lapatinib + Capecitabine N=198 (%)	Capecitabine N=191 (%)
Any AE leading to discontinuation	28 (14)	27 (14)
Diarrhea[1]	9 (5)	5 (3)
PPE	5 (3)	5 (3)
Nausea	3 (2)	2 (1)
Vomiting	2 (1)	2 (1)
Mucosal inflammation	2 (1)	1 (<1)
Neutropenia	2 (1)	1 (<1)
Pulmonary embolism	1 (<1)	2 (1)
Fatigue	2 (1)	0
CNS metastases	1 (<1)	1 (<1)
Dehydration	1 (<1)	1 (<1)
Disease progression	1 (<1)	1 (<1)

Data source: Study EGF 100151 report
1. Diarrhea includes incidences of diarrhea, loose stools and frequent bowel movements.

Reviewer: The proportion of AEs that lead to treatment termination was similar between the two arms in both interim and up date analyses. Diarrhea was the most common AE resulting in treatment termination with a similar incidence in both arms (5% for lapatinib + capecitabine and 3% for capecitabine). However, the dose of capecitabine was 25% higher for the control arm.

7.1.3.3 Other significant adverse events

7.1.3.3.1 7.1.3.3.1 Left Ventricular Ejection Fraction (LVEF) AEs

All LVEF AES, 6 in combination arm and one in capecitabine arm, are summarized in table below.

Table 48: Characteristics of LVEF AEs in study 100151 (SP, Nov 15 2005 cut-off)

	Lapatinib+ Capecitabine		Capecitabine	
	Nov 15 2005 N=164 (%)	Apr 3 2006 N=198 (%)	Nov 15 2005 N=152 (%)	Apr 3 2006 N=191 (%)
Subject with Events	6 (4)	7 (4)	1 (<1)	2 (1)
Number of Events	6	7	1	2
Event Characteristics, n				
Serious	4	5	1	2
Drug-related	6	7	0	0
Treatment termination	0	0	0	0
Fatal	0	0	0	0
Incidence per subject, n				
One	6	7	1	2
Two or more	0	0	0	0
Maximum Toxicity, n				
Grade 1	2	2	0	0
Grade 2	3	3	0	1
Grade 3	1	1	0	0
Grade 4 or 5	0	0	0	0
Not graded	0	1	1	1
Outcome, n				
Resolved	4	5	0	1
Resolved with sequelae	0	0	0	0
Not resolved	2	1	1	1
Fatal	0	0	0	0
Action Taken, n				
None	4	5	1	2
Dose adjusted	0	0	0	0
Temporarily interrupted	1	1	0	0
Permanently discontinued	0	0	0	0
Not applicable	1	1	0	0
Number of Interruptions, n				
One	1	1	0	0
Two or more	0	0	0	0
Time to Onset, days				
Mean (SD)	75.5 (53.11)	76.7 (48.59)	44.0 (NA)	42.5 (2.12)
Median (range)	61.0 (34-176)	79.0	44 (NA)	42.5
Duration, days				
Mean (SD)	52.3 (47.65)	39.4 (38.48)	NA	36 (NA)
Median (range)	36.0 (15-106)	28.0 (12-106)	NA	36.0 (36)

Data source: Study EGF 100151 report
NA = not applicable
Note: Subjects may be included in more than one category for Event characteristics, Outcome and Action taken.

Reviewer: Based on the data provided, overall analysis on relative change of LVEF from baseline indicated there is no decline in mean LVEF in either arm from baseline through 6 months.

Based on both interim and update analyses, there were 4% patients in lapatinib + capecitabine combination arm and 1% patient in capecitabine arm who experienced a decreased LVEF during the study. None of them was fatal or lead to treatment termination. At the time of interim analysis, two of the LVEF AEs were thought to be not reversible; but by the time of clinical update, only one LVEF AE was not reversible. However, five events in the lapatinib + capecitabine group were asymptomatic (grade 2 or less).

All seven events in the lapatinib + capecitabine group by the time of clinical update were considered drug related by the investigator. Four of them were classified as SAEs and the other two events of decreased LVEF did not meet the cardiac SAE criteria.

Amendment: After the completion of this NDA review (electronically filed on Mar 2, 2007), the applicant submitted additional safety reports on March 7th and 8th, 2007 for FDA to review. These reports provided follow up information of the one case of irreversible LVEF AEs at the time of safety update. Base on the additional information, the subject LEVF decreased from 60% to 48% on July 18, 2005, Day 83 after the first dose of lapatinib. The patient has previously received anthracycline and transtuzumab. The applicant has received follow up information on Dec 06, 2006 (after the Apr 3, 2006 cut-off date for safety update) that the LVEF was 50% on July 20, 2005 and 60% on Oct 18, 2005. This reviewer agrees that this LEVF AE has completely resolved.

7.1.3.3.2 7.1.3.3.2 Rash

AE rash were coded to three different MedDRA preferred terms as summarized in the table below.

Table 49: Study EGF 100151 AEs that recorded under all MedRA preferred terms for rash (SP, Nov 15 2005 cut-off)

Arm	Lapatinib+ Capecitabine		Capecitabine	
Cut-off date and total subjects	Nov 15 2005 N=164 n (%)	Apr 3 2006 N=198 (%)	Nov 15 2005 N=152 n (%)	Apr 3 2006 N=191 (%)
Any Rash AE	45 (27)	55 (28)	23 (15)	26 (14)
Rash	34 (21)	39 (20)	15 (10)	14 (7)
Erythema	8 (5)	11 (6)	9 (6)	12 (6)
Acne	10 (6)	13 (7)	0	0

Data source: Study EGF 100151 report

All three types above AEs have been combined here for evaluation of total number of subjects experienced rash during the study, as shown in Table below.

Table 50: Characteristics of rash (SP, Nov 15 2005 cut-off)

Arm	Lapatinib+ Capecitabine		Capecitabine	
Cut-off date and total subjects	Nov 15 2005 N=164 n (%)	Apr 3 2006 N=198 (%)	Nov 15 2005 N=152 n (%)	Apr 3 2006 N=191 (%)
Subjects with Events	45 (27)	55 (28)	23 (15)	26 (14)
Number of Events	81	99	35	37
Event Characteristics, n	**N = 45**	**N = 55**	**N = 23**	**N = 26**
Serious	1 (2)	1 (2)	1 (4)	1 (4)
Considered drug-related	42 (93)	49 (99)	21 (91)	23 (88)
Leading to withdrawal	2 (4)	1 (2)	0	0
Fatal	0	0	0	0
Incidence per subject, n	**N = 45**	**N = 55**	**N = 23**	**N = 26**
One	29 (64)	33 (60)	15 (65)	19 (73)
Two	5 (11)	10 (18)	5 (22)	4 (15)
Three or more	11 (24)	12 (22)	3 (13)	3 (12)
Maximum Toxicity, n	**N = 45**	**N = 55**	**N = 23**	**N = 26**
Grade 1	32 (71)	39 (71)	14 (61)	17 (65)
Grade 2	11 (24)	13 (24)	7 (30)	7 (27)
Grade 3	2 (4)	3 (5)	2 (9)	2 (8)
Grade 4 or 5	0	0	0	0
Outcome, n	**N = 45**	**N = 55**	**N = 23**	**N = 26**
Resolved	35 (78)	42 (76)	18 (78)	20 (77)
Resolved with sequelae	1 (2)	1 (2)	0	0
Not resolved	15 (33)	20 (36)	7 (30)	8 (31)
Fatal	0	0	0	0
Action Taken, n	**N = 45**	**N = 55**	**N = 23**	**N = 26**
None	43 (96)	52 (95)	20 (87)	23 (88)
Dose adjusted	2 (4)	2 (4)	5 (22)	4 (15)
Temporarily interrupted	8 (18)	7 (13)	2 (9)	2 (8)
Permanently discontinued	3 (7)	1 (2)	0	0
NA	0	1 (2)	0	0
Treatment Interruptions, n	**N = 45**	**N -55**	**N = 23**	**N = 26**
One	6 (13)	7 (13)	1 (4)	1 (4)
Two	2 (4)	0	1 (4)	1 (4)
Three or more	0	0	0	0
Time of Onset, Days, n	**N = 45**	**N = 55**	**N = 23**	**N = 26**
Mean (SD)	36.4 (41.05)	35.9 (41.05)	37.4 (53.49)	36.9 (52.11)
Median (range)	22.0 (2-175)	22.0 (2-175)	16.0 (1-225)	21.0 (1-225)
Duration Days, n	**N = 45**	**N = 55**	**N = 23**	**N = 26**
Mean (SD)	23.2 (19.43)	25.0 (26.37)	43.9 (60.74)	25.4 (21.72)
Median (range)	21.0 (1-72)	20.0 (1-136)	22.0 (3-253)	21.0 (3-91)

Data source: Study EGF 100151 report
Note: Subjects may be included in more than one category for Event characteristics, Outcome and Action taken.

Reviewer: More subjects in the lapatinib + capecitabine arm (27%) had rash than in the capecitabine arm (15%). This difference was mainly due to increased incidences of grade 1 in the combination arm.

7.1.4 Other Search Strategies

The AE are common for both capecitabine and lapatinib are summarized as below.

7.1.4.1 Diarrhea

The incidence of all grade, server and fatal diarrhea, as well as diarrhea that cause treatment termination, were summarized in relevant sections. The characteristics of diarrhea AEs are summarized in table below.

Table 51: Table 52: Characteristics of Diarrhea AEs (SP, Nov 15, 2006 cut-off)

Arm	Lapatinib+ Capecitabine		Capecitabine	
Cut-off date and total subjects	Nov 15 2005 N=164 n (%)	Apr 3 2006 N=198 (%)	Nov 15 2005 N=152 n (%)	Apr 3 2006 N=191 (%)
Subjects with Events	98 (60)	128 (65)	60 (39)	76 (40)
Number of Events	294	360	147	170
Event Characteristics, n	**N = 98**	**N = 128**	**N = 60**	**N = 76**
Serious	11 (11)	13 (10)	12 (20)	12 (16)
Considered drug-related	92 (94)	119 (93)	55 (92)	71 (83)
Leading to withdrawal	7 (7)	7 (5)	1 (2)	1 (1)
Fatal	0	0	1 (2)	1 (1)
Incidence per subjects	**N = 98**	**N = 128**	**N = 60**	**N = 76**
One	36 (37)	51 (40)	28 (47)	37 (49)
Two	17 (17)	23 (18)	12 (20)	15 (20)
Three or more	45 (46)	54 (42)	20 (33)	24 (32)
Maximum Toxicity, n	**N = 98**	**N = 128**	**N = 60**	**N = 76**
Grade 1	44 (45)	61 (48)	21 (35)	30 (39)
Grade 2	33 (34)	40 (31)	22 (37)	27 (36)
Grade 3	19 (19)	25 (20)	17 (28)	19 (25)
Grade 4	2 (2)	0	0	0
Grade 5	0	0	1 (2)	0
Outcome, n	**N = 98**	**N = 128**	**N = 60**	**N = 76**
Resolved	90 (92)	114 (89)	57 (95)	72 (95)
Resolved with sequelae	4 (4)	7 (5)	1 (2)	1 (1)
Not resolved	19 (19)	24 (19)	8 (13)	7 (9)
Fatal	0	0	1 (2)	1 (1)
Treatment change, n	**N = 98**	**N = 128**	**N = 60**	**N = 76**
None	91 (93)	122 (95)	44 (73)	58 (76)
Dose adjusted	14 (14)	16 (13)	14 (23)	19 (25)
Temporarily interrupted	21 (21)	25 (20)	14 (23)	19 (25)
Permanently discontinued	8 (8)	9 (7)	4 (7)	5 (7)
Not applicable	3 (3)	3 (2)	5 (8)	4 (5)
Treatment interruptions, n	**N = 98**	**N = 128**	**N = 60**	**N = 76**
One	13 (13)	16 (12)	12 (20)	17 (22)
Two	6 (6)	6 (5)	2 (3)	2 (3)
Three or more	2 (2)	3 (2)	0	0
Time of Onset Days, n	**N = 98**	**N = 128**	**N = 60**	**N = 76**
Mean (SD)	18.2 (28.93)	20.1 (29.31)	22.4 (18.14)	23.6 (22.95)
Median (range)	8.0 (1-161)	9.0 (1-161)	16.0 (1-106)	15.5 (1-118)
Duration Days, n	**N = 98**	**N = 128**	**N = 60**	**N = 76**

Arm	Lapatinib+ Capecitabine		Capecitabine	
Cut-off date and total subjects	Nov 15 2005 N=164 n (%)	Apr 3 2006 N=198 (%)	Nov 15 2005 N=152 n (%)	Apr 3 2006 N=191 (%)
Mean (SD)	23.9 (50.71)	20.0 (33.97)	18.0 (47.06)	16.1 (43.2)
Median (range)	7.0 (1-367)	7.0 (1-228)	7.0 (1-329)	6.0 (1-329)

Data source: Study EGF 100151 report
Note: Subjects may be included in more than one category for event characteristics, outcome and action taken.
For purposes of this summary diarrhea includes preferred terms of diarrhea, diarrhea hemorrhagic and diarrhea Infectious.

Reviewer: More subjects in the lapatinib-capecitabine combination arm (98 of 164 subjects; 60%) had diarrhea than in the capecitabine arm (60 of 152 subjects; 39%); whereas more subjects in the capecitabine group (20%) than in the lapatinib + capecitabine group (11%) had a diarrhea SAE and one subject in the capecitabine group had fatal diarrhea with vomiting and small bowel obstruction (see fatal AEs). Eight (5%) subjects in the combination group and 4 (3%) subject in the monotherapy group withdrew from the study due to diarrhea. The difference in the incidence of diarrhea AEs was due to an increased number of grade 1 or 2 toxicity reports in the lapatinib + capecitabine group.

7.1.4.2 Palmar-Plantar Erythrodysesthesia (PPE)

The characteristic of PPE Events are summarized in the table below.

Table 53: Characteristics of Palmar-Plantar Erythrodysesthesia (SP, Nov 15 2005 cut-off)

Arm	Lapatinib+ Capecitabine		Capecitabine	
Cut-off date and total subjects	Nov 15 2005 N=164 n (%)	Apr 3 2006 N=198 (%)	Nov 15 2005 N=152 n (%)	Apr 3 2006 N=191 (%)
Subjects with Events	80 (49)	105 (53)	74 (49)	97 (51)
Number of Events	176	268	181	260
Event Characteristics, n	**N = 80**	**N = 105**	**N = 74**	**N =97**
Serious	0	0	0	0
Considered drug-related	72 (90)	97 (92)	71 (96)	93 (96)
Leading to withdrawal	1 (1)	3 (2)	1 (1)	3 (3 (3)
Fatal	0	0	0	0
Incidence per subject, n	**N = 80**	**N = 105**	**N = 74**	**N = 97**
One	35 (44)	43 (41)	26 (35)	37 (28)
Two	20 (25)	21 (20)	20 (27)	21 (22)
Three or more	25 (31)	41 (39)	28 (38)	39 (40)
Maximum Toxicity, n	**N = 80**	**N = 105**	**N = 74**	**N = 97**
Grade 1	16 (20)	25 (24)	19 (26)	22 (23)
Grade 2	52 (65)	57 (54)	39 (53)	48 (49)
Grade 3	12 (15)	23 (22)	16 (22)	27 (28)
Grade 4 or 5	0	0	0	0
Outcome, n	**N = 80**	**N = 105**	**N = 74**	**N = 97**
Resolved	63 (79)	83 (79)	56 (76)	76 (78)
Resolved with sequelae	7 (9)	8 (8)	7 (9)	7 (7)
Not resolved	38 (48)	52 (50)	36 (49)	46 (47)

Arm	Lapatinib+ Capecitabine		Capecitabine	
Cut-off date and total subjects	Nov 15 2005 N=164 n (%)	Apr 3 2006 N=198 (%)	Nov 15 2005 N=152 n (%)	Apr 3 2006 N=191 (%)
Fatal	0	0	0	0
Action Taken, n	**N = 80**	**N = 105**	**N = 74**	**N = 97**
None	60 (75)	84 (80)	64 (86)	84 (87)
Dose adjusted	24 (30)	35 (33)	22 (30)	30 (31)
Temporarily interrupted	27 (34)	41 (39)	19 (26)	34 (35)
Permanently discontinued	4 (5)	5 (5)	3 (4)	5 (5)
NA	0	0	3 (4)	2 (3)
Treatment Interruptions, n	**N = 80**	**N = 105**	**N = 74**	**N = 97**
One	21 (26)	27 (26)	16 (22)	25 (26)
Two	5 (6)	12 (11)	1 (1)	6 (6)
Three or more	1 (1)	2 (2)	2 (3)	3 (3)
Time of Onset Days, n	**N = 80**	**N = 105**	**N = 74**	**N = 97**
Mean (SD)	61.1 (60.80)	56.0 (55.96)	30.8 (31.15)	32.4 (35.39)
Median (range)	43.0 (1-425)	40.0 (1-425)	16.5 (1-152)	21.0 (1-244)
Duration Days, n	**N = 80**	**N = 105**	**N = 74**	**N = 97**
Mean (SD)	34.5 (29.30)	33.9 (28.72)	40.8 (53.31)	47.8 (72.88)
Median (range)	24.0 (5-156)	25.5 (5-156	15.0 (2-272)	17.0 (2-430)

Data source: Study EGF 100151 report
Note: Subjects may be included in more than one category for Event characteristics, Outcome and Action taken.

Reviewer: Approximately half the subjects in the study EGF 100151 had a PPE event (49% in both arms); this incidence was similar to that previously reported for capecitabine. However, the capecitabine dose for the lapatinib combination arm was 20% less than the control arm and the label reported dose. The majority PPE events were of grade 1 or 2 and resolvable. Both the median duration and the time to onset were longer in the combination arm than in the capecitabine arm (24 days versus 15 days and 43 days versus 16.5 days, respectively). A few subjects in either treatment group (4 in combination arm and 3 in capecitabine arm) terminated study treatment due to PPE.

7.1.5 Common Adverse Events

Common AEs (≥5% subjects on the lapatinib combination arm) by MedDRA term, regardless of relationship to investigational product, giving in the order of decreasing frequency are summarized in the table below.

Table 54: Study EGF 100151 Common AEs regardless relationship (SP, Nov 15 2005 cut-off)

MedDRA Preferred Terms	Lapatinib + capecitabine N = 164				Capecitabine N = 152			
	All	%	G3-4	%	All	%	G3-4	%
Diarrhea	98	60	21	13	60	39	17	11
Palmar-plantar erythrodysesthesia syndrome	80	49	12	7	74	49	16	11
Nausea	72	44	3	2	63	41	3	2
Rash	45	27	2	1	23	15	2	1
Vomiting	43	26	3	2	36	24	3	2
Fatigue	29	18	3	2	41	27	6	4
Anorexia	25	15	1	1	30	20	1	1

MedDRA Preferred Terms	Lapatinib + capecitabine N = 164				Capecitabine N = 152			
	All	%	G3-4	%	All	%	G3-4	%
Stomatitis	24	15	0	0	18	12	1	1
Pain in extremity	20	12	1	1	12	8	1	1
Dyspepsia	18	11	0	0	5	3	0	0
Mucosal inflammation	18	11	0	0	19	13	3	2
Dyspnea	18	11	5	3	10	7	3	2
Dry skin	18	11	0	0	8	5	0	0
Back pain	17	10	2	1	9	6	1	1
Abdominal pain	16	10	2	1	25	16	2	1
Constipation	16	10	0	0	17	11	1	1
Insomnia	16	10	1	1	9	6	0	0
Headache	15	9	0	0	19	13	2	1
Abdominal pain upper	12	7	0	0	8	5	0	0
Arthralgia	12	7	1	1	6	4	0	0
Edema peripheral	11	7	1	1	5	3	1	1
Bone pain	11	7	2	1	6	4	1	1
Cough	11	7	0	0	13	9	0	0
Epistaxis	11	7	0	0	4	3	0	0
Asthenia	10	6	0	0	18	12	3	2
Anemia	9	5	0	0	7	5	1	1
Chest pain	8	5	1	1	4	3	1	1
Pyrexia	8	5	0	0	12	8	0	0
Dysgeusia	8	5	0	0	3	2	0	0
Lethargy	8	5	2	1	4	3	0	0

Data source: Study EGF 100151 report

Reviewer: Diarrhea, palmar-plantar erythrodysesthesia (PPE), nausea, rash, vomiting and fatigue were the most common AEs reported for the combination arm. Diarrhea and rash were more common on the lapatinib + capecitabine arm (60% versus 39% and 27% versus 15%, respectively). Incidence of PPE, nausea and vomiting were similar between the two treatment arms, with the notation that capecitabine is 25% higher for the control arm. On the other hand, fatigue was more common in the capecitabine group (27% versus 18%), as were anorexia (20% vs. 15%), abdominal pain (16% vs. 10%), and asthenia (12% vs. 6%). No interstitial pneumonia or pneumonitis was observed during this study.

For further details, please sea the list of all AEs recorded during study EGF 100151 and summarized by body system in section 10.1.1.5.12.

The 120 day safety update of common AE analysis was conducted in SP population and based on the data from Apr 3 2006 cut-off, as shown in table below.

Table 55: EGF 100151 Common AEs (≥ 5%, regardless relationship) update (SP, Apr 3 2006 cut-off)

MedDRA Preferred Terms	Lapatinib + Capecitabine N = 198				Capecitabine N = 191			
	All	%	G3-4	%	All	%	G3-4	%
Diarrhea	128	65	27	14	76	40	19	10
Palmar-plantar erythrodysesthesia	105	53	23	12	97	51	27	14
Nausea	87	44	3	2	83	43	3	2
Rash	55	28	3	2	26	14	2	1
Vomiting	52	26	4	2	41	21	3	2
Fatigue	46	23	5	3	47	25	7	4
Mucosal inflammation	29	15	0	0	23	12	3	2
Stomatitis	27	14	0	0	21	11	1	1
Anorexia	27	14	1	1	37	19	1	1
Abdominal pain	25	13	2	1	30	16	2	1
Pain in extremity	23	12	2	1	14	7	1	1
Dyspnea	23	12	6	3	16	8	4	2
Dyspepsia	22	11	1	1	6	3	0	0
Back pain	22	11	2	1	11	6	1	1
Constipation	20	10	0	0	22	12	2	1
Asthenia	20	10	3	2	24	13	3	2
Headache	20	10	0	0	26	14	2	1
Insomnia	20	10	1	1	11	6	0	0
Dry skin	20	10	0	0	11	6	0	0
Abdominal pain upper	17	9	0	0	12	6	0	0
Pyrexia	16	8	0	0	12	6	0	0
Epistaxis	15	8	0	0	4	2	0	0
Arthralgia	14	7	1	1	8	4	0	0
Cough	14	7	0	0	16	8	0	0
Bone pain	13	7	1	1	8	4	1	1
Edema peripheral	11	6	1	1	7	4	1	1
Anemia	10	5	0	0	10	5	2	1
Lacrimation increased	10	5	0	0	6	3	0	0
Chest pain	10	5	1	1	6	3	1	1
Hypokalemia	10	5	6	3	6	3	2	1
Muscle spasms	10	5	0	0	3	2	0	0
Nail disorder	10	5	0	0	4	2	0	0
Pruritus	10	5	0	0	5	3	0	0
Conjunctivitis	9	5	0	0	3	2	0	0
Mouth ulceration	9	5	0	0	4	2	0	0
Dehydration	9	5	5	3	8	4	2	1
Dysgeusia	9	5	0	0	6	3	0	0

Data source: Study EGF 100151 report

Reviewer: The updated common AE are similar to the interim analysis, both incidence and difference between the two arms.

The common (≥5%) AEs observed in Studies EGF 20002 and EGF 20008 regardless treatment relationships, are summarized as below:

Table 56: Common AEs (≥5%) in studies EGF20002 and EGF 20008 regardless treatment relationship

Body System Preferred Term	Lapatinib 1250mg (N=34)	Lapatinib 1500mg (N=273)	All Subjects (N=307)
ANY EVENT	33 (97%)	264 (97%)	297 (97%)
Gastrointestinal disorders			
Abdominal pain	3 (9%)	31 (11%)	34 (11%)
Constipation	3 (9%)	25 (9%)	28 (9%)
Diarrhea[1]	15 (44%)	164 (60%)	179 (58%)
Dyspepsia	3 (9%)	14 (5%)	17 (6%)
Nausea	9 (26%)	107 (39%)	116 (38%)
Stomatitis	1 (3%)	17 (6%)	18 (6%)
Vomiting	3 (9%)	64 (23%)	67 (22%)
General disorders and administration site conditions			
Asthenia	1 (3%)	18 (7%)	19 (6%)
Chest pain	1 (3%)	14 (5%)	15 (5%)
Chills	2 (6%)	12 (4%)	14 (5%)
Edema, peripheral	2 (6%)	18 (7%)	20 (7%)
Fatigue	14 (41%)	85 (31%)	99 (32%)
Pain	1 (3%)	15 (5%)	16 (5%)
Pyrexia	5 (15%)	28 (10%)	33 (11%)
Infections and infestations			
Upper respiratory tract infection	3 (9%)	11 (4%)	14 (5%)
Urinary tract infection	2 (6%)	17 (6%)	19 (6%)
Investigations			
Weight decreased	4 (12%)	20 (7%)	24 (8%)
Metabolism and nutrition disorders			
Anorexia	5 (15%)	47 (17%)	52 (17%)
Dehydration	1 (3%)	13 (5%)	14 (5%)
Musculoskeletal and connective tissue disorders			
Arthralgia	3 (9%)	22 (8%)	25 (8%)
Back pain	4 (12%)	28 (10%)	32 (10%)
Pain in extremity	1 (3%)	15 (5%)	16 (5%)
Nervous system disorders			
Headache	2 (6%)	32 (12%)	34 (11%)
Dizziness	2 (6%)	14 (5%)	16 (5%)
Psychiatric disorders			
Insomnia	1 (3%)	21 (8%)	22 (7%)
Respiratory, thoracic, and mediastinal disorders			
Cough	6 (18%)	28 (10%)	34 (11%)
Dyspnea	5 (15%)	44 (16%)	49 (16%)
Epistaxis	3 (9%)	14 (5%)	17 (6%)
Skin and subcutaneous tissue disorders			
Dermatitis acne form	1 (3%)	24 (9%)	25 (8%)
Dry skin	3 (9%)	18 (7%)	21 (7%)
Pruritus	4 (12%)	33 (12%)	37 (12%)
Rash	2	17 (50%)	98 (36%)

Source: Study EGF20002 and 2008 reports.
1. Diarrhea included diarrhea, loose stools, and frequent bowel movements.
2. Rash included acne, erythema, eczema, rash papular, dermatitis, rash, folliculitis, and rash pustular.

7.1.6 Less Common Adverse Events

Table 57: Study EGF 100151 less common (<5%) AEs and SAEs regardless of relationship (SP, Apr 3 2006 cut-off)

MedDRA Prefered Terms	Lapatinib + capecitabine N = 198				Capecitabine N = 191			
	All	%	G3-4	%	All	%	G3-4	%
Nail infection	8	4	1	1	4	2	0	0
Nasopharyngitis	8	4	0	0	13	7	0	0
Blood bilirubin increased	8	4	1	1	2	1	0	0
Dizziness	8	4	0	0	15	8	2	1
Lethargy	8	4	2	1	5	3	0	0
Anxiety	8	4	1	1	3	2	0	0
Alopecia	8	4	0	0	6	3	0	0
Dry mouth	7	4	0	0	6	3	1	1
Hyperbilirubinaemia	7	4	1	1	4	2	2	1
Localized infection	7	4	0	0	2	1	0	0
Decreased appetite	7	4	0	0	4	2	0	0
Myalgia	7	4	1	1	7	4	0	0
Dermatitis acne form	7	4	1	1	0	0	0	0
Leukopenia	6	3	0	0	3	2	1	1
Neutropenia	6	3	4	2	15	8	5	3
Hemorrhoids	6	3	0	0	2	1	0	0
Upper respiratory tract infection	6	3	0	0	6	3	2	1
Blood alkaline phosphatase increased	6	3	1	1	2	1	0	0
Ejection fraction decreased	6	3	1	1	1	1	0	0
Weight decreased	6	3	0	0	9	5	0	0
Neuropathy peripheral	6	3	0	0	5	3	0	0
Paraesthesia	6	3	0	0	9	5	0	0
Dysuria	6	3	1	1	3	2	0	0
Skin hyperpigmentation	6	3	0	0	7	4	0	0
Vertigo	5	3	0	0	5	3	0	0
Dry eye	5	3	0	0	3	2	0	0
Flatulence	5	3	0	0	3	2	0	0
Bronchitis	5	3	0	0	2	1	0	0
Rhinitis	5	3	0	0	5	3	0	0
Urinary tract infection	5	3	1	1	7	4	0	0
Hemoglobin decreased	5	3	0	0	3	2	0	0
Musculoskeletal chest pain	5	3	1	1	7	4	0	0
Depression	5	3	2	1	6	3	0	0
Rhinorrhoea	5	3	0	0	1	1	0	0
Onycholysis	5	3	0	0	2	1	0	0
Thrombocytopenia	4	2	1	1	4	2	4	2
Eye irritation	4	2	0	0	2	1	0	0
Vision blurred	4	2	0	0	4	2	0	0
Dysphasia	4	2	0	0	2	1	0	0
Gastrooesophageal reflux disease	4	2	1	1	1	1	0	0
Lip ulceration	4	2	0	0	1	1	0	0
Chills	4	2	0	0	4	2	0	0
Pain	4	2	0	0	5	3	1	1

MedDRA Prefered Terms	Lapatinib + capecitabine N = 198				Capecitabine N = 191			
	All	%	G3-4	%	All	%	G3-4	%
Alanine aminotransferase increased	4	2	0	0	2	1	0	0
Aspartate aminotransferase increased	4	2	1	1	3	2	0	0
Depressed mood	4	2	0	0	0	0	0	0
Vaginal hemorrhage	4	2	0	0	0	0	0	0
Pharyngolaryngeal pain	4	2	0	0	2	1	0	0
Pain of skin	4	2	0	0	1	1	0	0
Rash macular	4	2	0	0	0	0	0	0
Tachycardia	3	2	0	0	1	1	0	0
Visual disturbance	3	2	0	0	5	3	0	0
Abdominal distension	3	2	0	0	5	3	1	1
Cheilitis	3	2	0	0	1	1	0	0
Gastritis	3	2	0	0	2	1	0	0
Lip blister	3	2	0	0	1	1	0	0
Lip dry	3	2	0	0	1	1	0	0
Edema	3	2	0	0	1	1	0	0
Lower respiratory tract infection	3	2	0	0	1	1	0	0
Oral candidiasis	3	2	0	0	0	0	0	0
Paronychia	3	2	0	0	2	1	0	0
Sinusitis	3	2	0	0	2	1	0	0
Muscular weakness	3	2	1	1	2	1	1	1
Hypoaesthesia	3	2	0	0	1	1	0	0
Neuropathy	3	2	0	0	2	1	0	0
Breast pain	3	2	0	0	2	1	1	1
Nasal ulcer	3	2	0	0	0	0	0	0
Productive cough	3	2	0	0	2	1	0	0
Blister	3	2	1	1	2	1	0	0
Hyperhidrosis	3	2	0	0	2	1	0	0
Onychoclasis	3	2	0	0	0	0	0	0
Skin lesion	3	2	0	0	0	0	0	0
Lymphopenia	2	1	0	0	1	1	0	0
Sinus tachycardia	2	1	0	0	1	1	0	0
Ear pain	2	1	0	0	1	1	0	0
Eye Pruritus	2	1	0	0	0	0	0	0
Ocular icterus	2	1	0	0	0	0	0	0
Chapped lips	2	1	0	0	1	1	0	0
Gingival pain	2	1	0	0	1	1	0	0
Glossodynia	2	1	0	0	0	0	0	0
Haematochezia	2	1	0	0	0	0	0	0
Face edema	2	1	0	0	1	1	0	0
Impaired healing	2	1	0	0	0	0	0	0
Hepatic function abnormal	2	1	1	1	0	0	0	0
Catheter related infection	2	1	1	1	0	0	0	0
Erysipelas	2	1	1	1	0	0	0	0
Herpes simplex	2	1	0	0	3	2	0	0
Influenza	2	1	1	1	2	1	0	0
Lymphangitis	2	1	0	0	1	1	0	0
Skin infection	2	1	0	0	3	2	0	0
Tooth abscess	2	1	0	0	1	1	0	0
Viral infection	2	1	0	0	1	1	0	0

MedDRA Prefered Terms	Lapatinib + capecitabine N = 198				Capecitabine N = 191			
	All	%	G3-4	%	All	%	G3-4	%
Rib fracture	2	1	0	0	0	0	0	0
Skin laceration	2	1	0	0	0	0	0	0
Blood albumin decreased	2	1	0	0	0	0	0	0
Creatinine renal clearance decreased	2	1	0	0	0	0	0	0
Platelet count decreased	2	1	0	0	0	0	0	0
White blood cell count decreased	2	1	0	0	2	1	1	1
Hyperglycaemia	2	1	0	0	4	2	0	0
Hyperkalaemia	2	1	0	0	0	0	0	0
Hyponatraemia	2	1	1	1	2	1	1	1
Buttock pain	2	1	0	0	0	0	0	0
Musculoskeletal stiffness	2	1	0	0	0	0	0	0
Neck pain	2	1	0	0	2	1	0	0
Shoulder pain	2	1	0	0	3	2	0	0
Cancer pain	2	1	2	1	0	0	0	0
Metastases to central nervous system	2	1	1	1	0	0	0	0
Hyperaesthesia	2	1	0	0	1	1	0	0
Neuralgia	2	1	1	1	1	1	0	0
Neurotoxicity	2	1	1	1	5	3	1	1
Parosmia	2	1	0	0	0	0	0	0
Peripheral sensory neuropathy	2	1	0	0	12	6	0	0
Syncope	2	1	1	1	1	1	1	1
Pollakiuria	2	1	0	0	1	1	0	0
Pelvic pain	2	1	0	0	3	2	0	0
Dyspnoea exertional	2	1	1	1	0	0	0	0
Pulmonary embolism	2	1	2	1	1	1	1	1
Rhinitis allergic	2	1	0	0	1	1	0	0
Exfoliative rash	2	1	0	0	2	1	1	1
Ingrowing nail	2	1	0	0	1	1	0	0
Palmar erythema	2	1	0	0	0	0	0	0
Rash erythematous	2	1	0	0	1	1	0	0
Skin chapped	2	1	0	0	2	1	0	0
Skin discolouration	2	1	0	0	2	1	0	0
Skin fissures	2	1	1	1	0	0	0	0
Skin ulcer	2	1	1	1	1	1	0	0
Xeroderma	2	1	0	0	0	0	0	0
Hot flush	2	1	0	0	2	1	0	0
Lymphoedema	2	1	1	1	2	1	0	0
Pallor	2	1	0	0	0	0	0	0
Granulocytopenia	1	1	0	0	0	0	0	0
Haematotoxicity	1	1	0	0	0	0	0	0
Leukocytosis	1	1	0	0	0	0	0	0
Microcytic anemia	1	1	0	0	0	0	0	0
Arrhythmia supraventricular	1	1	0	0	0	0	0	0
Bundle branch block right	1	1	0	0	0	0	0	0
Cardio-respiratory arrest	1	1	0	0	0	0	0	0
Palpitations	1	1	0	0	2	1	0	0
Pericarditis	1	1	0	0	0	0	0	0
Prinzmetal angina	1	1	0	0	0	0	0	0
Supraventricular extrasystoles	1	1	0	0	0	0	0	0