

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-059**

**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

**NDA/Serial Number:** N022059 / 000

**Drug Name:** Tykerb (lapatinib) Tablets, 1250 mg/day once daily

**Indication(s):** In combination of capecitabine (Xeloda), the drug is seeking indication for the treatment of advanced or metastatic breast cancer in patients who have HER2 (ErbB2) tumor over-expression and have received prior therapy including anthracyclines, taxanes, and trastuzumab

**Applicant:** GlaxoSmithKline

**Date(s):** Submission date: September 13, 2006  
PDUFA due date: March 13, 2007  
Review completion date: March 1, 2007

**Review Priority:** Priority

**Biometrics Division:** Division of Biometrics 5 (HFD-711)

**Statistical Reviewer:** Chia-Wen Ko, Ph.D.

**Concurring Reviewers:** Rajeshwari Sridhara, Ph.D., Team Leader  
Aloka Chakravarty, Ph.D., Division Director

**Medical Division:** Oncology Drug Products (HFD-150)

**Clinical Team:** Qin Ryan, M.D. & Amna Ibrahim, M.D.

**Project Manager:** Kim Robertson

**Keywords:** add-on design, data monitoring committee, open-label, multi-center, intent-to-treat, per protocol, log-rank test, time to progression, progression free survival, response rate, duration of response, survival analysis, Kaplan-Meier curve, missing data, censoring, multiple endpoints, interim analysis, subgroup analyses, sensitivity analyses

# Table of Contents

<b>1. EXECUTIVE SUMMARY .....</b>	<b>3</b>
1.1 CONCLUSIONS AND RECOMMENDATIONS .....	3
1.2 BRIEF OVERVIEW OF CLINICAL STUDIES .....	3
1.3 STATISTICAL ISSUES AND FINDINGS .....	4
<b>2. INTRODUCTION .....</b>	<b>8</b>
2.1 OVERVIEW.....	8
2.1.1 <i>Background</i> .....	8
2.1.2 <i>Clinical Studies</i> .....	9
2.1.3 <i>Major Statistical Issues</i> .....	10
2.2 DATA SOURCES .....	11
<b>3. STATISTICAL EVALUATION .....</b>	<b>11</b>
3.1 EVALUATION OF EFFICACY .....	11
3.1.1 <i>Study EGF100151</i> .....	12
3.1.1.1 Study Design.....	12
3.1.1.2 Study Objectives.....	13
3.1.1.3 Definition of Efficacy Endpoints.....	13
3.1.1.4 Statistical Analyses.....	14
3.1.1.5 Analysis Populations.....	15
3.1.1.6 Sample Size Justification .....	15
3.1.1.7 Interim Analysis.....	16
3.1.1.8 Efficacy Results and Conclusions .....	17
3.1.1.8.1 Disposition of Patients.....	17
3.1.1.8.2 Demographics and Other Baseline Characteristics .....	19
3.1.1.8.3 Efficacy Results .....	20
3.1.1.8.3.1 Time to Progression .....	20
3.1.1.8.3.1.1 Results reviewed by Independent Data Monitoring Committee.....	21
3.1.1.8.3.1.2 Results based on data submitted to the Agency .....	22
3.1.1.8.3.1.3 Investigator versus Independent Reviews and Interim versus Updated in TTP .....	25
3.1.1.8.3.2 Overall Survival .....	38
3.1.1.8.3.3 Progression Free Survival and 6-Month Progression Free Survival .....	39
3.1.1.8.3.4 Response Rate .....	40
3.1.1.8.3.5 Clinical Benefit Response Rate .....	42
3.1.1.8.3.6 Duration of Response.....	42
3.1.1.8.3.7 Other Efficacy Results.....	42
3.1.1.8.4 Conclusions for Efficacy .....	45
3.2 EVALUATION OF SAFETY.....	46
<b>4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS .....</b>	<b>46</b>
4.1 GENDER, RACE AND AGE .....	46
<b>5. SUMMARY AND CONCLUSIONS .....</b>	<b>47</b>
5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE .....	48
5.2 CONCLUSIONS AND RECOMMENDATIONS .....	49
<b>SIGNATURES/DISTRIBUTION LIST.....</b>	<b>50</b>

## 1. EXECUTIVE SUMMARY

This NDA submission is seeking approval of lapatinib by demonstrating that Tykerb (lapatinib), in combination of capecitabine, is effective and safe for the treatment of patients with advanced or metastatic breast cancer whose tumors over-express ErbB2 and who have received prior therapy including anthracyclines, taxanes, and trastuzumab. This submission includes data and study reports for three clinical studies in breast cancer patients (Studies EGF100151, EGF20002, and EGF20008). The Study EGF100151 is the pivotal Phase III randomized trial with dose regimen and patient population for this indication, and therefore is used as basis of this review.

### 1.1 Conclusions and Recommendations

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 trasztuzumab. 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.

### 1.2 Brief Overview of Clinical Studies

The sponsor submitted data and study reports on the following 3 clinical studies in breast cancer patients:

1. Study EGF100151: Phase III randomized multi-center, open-label trial comparing efficacy and safety between two treatment groups (lapatinib + capecitabine and placebo + capecitabine) in ErbB2 over-expressed advanced or metastatic breast cancer patients. Study participants were randomized on a 1:1 ratio to receive either 2500 mg/m<sup>2</sup>/day capecitabine for 14 days every 21 days or 2000 mg/m<sup>2</sup>/day capecitabine for 14 days every 21 days plus 1250 mg lapatinib once daily continuously. Patients were treated until disease progression or until unacceptable toxicity had occurred. Total n = 324 patients as of 15 November 2005 (interim analysis cut-off date). The final number of enrolled patients is 399 as the study stopped its enrollment on 03 April 2006. The primary

endpoint was time to progression, defined as time from randomization to disease progression or death due to breast cancer.

2. Study EGF20002: A Phase II open-label, multi-center, single-arm study of lapatinib as a single agent therapy in patients with advanced or metastatic breast cancer who have progressed while receiving trastuzumab-containing regimens. A total of 78 patients self-administered oral lapatinib at a dose of 1250 mg or 1500 mg once daily until disease progression or withdraw from the study. The primary endpoint for this Phase II study was tumor response rate.
3. Study EGF20008: A Phase II open-label, multi-center, single-arm study of lapatinib as a single agent therapy in patients with advanced or metastatic breast cancer who have progressed while receiving trastuzumab-containing regimens. Lapatinib 1500 mg administered once daily to a total of 229 female patients with advanced or metastatic breast cancer and refractory to anthracycline-, taxane- and capecitabine-containing regimens. The primary endpoint of response rate was evaluated in two cohorts – Cohort A of 140 patients with ErbB2 over-expressing tumors, and Cohort B of 89 patients without ErbB2 over-expressing tumors.

Study EGF100151 is used as the basis for the statistical review and evaluation since it is the only controlled clinical trial pertinent to the indication. Both data on 324 patients as of interim analysis cut-off and data on the total enrolled 399 patients are reviewed.

### 1.3 Statistical Issues and Findings

This is a NDA submission seeking approval of lapatinib 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 trastuzumab. Study EGF100151 was conducted as the Phase III trial intended for such indication.

Study EGF100151 is a Phase III randomized multi-center, open-label trial in ErbB2 over-expressed advanced or metastatic breast cancer patients. Study participants were randomized on a 1:1 ratio to receive either 2500 mg/m<sup>2</sup>/day capecitabine for 14 days every 21 days or 2000 mg/m<sup>2</sup>/day capecitabine for 14 days every 21 days plus 1250 mg lapatinib once daily continuously. Patients were treated until disease progression or until unacceptable toxicity had occurred. Safety and efficacy assessments were performed every 6 weeks for the first 24 weeks, then every 12 weeks and at the end of treatment. The primary efficacy endpoint was time to progression, defined as time from randomization to disease progression or death due to breast cancer. Secondary efficacy endpoints include progression free survival, overall survival, response rate, clinical benefit, and duration of response. The two treatment groups were compared in terms of time to event endpoints including time to progression, progression free survival, and overall survival using log-rank test stratified for stage and site of disease. Overall response rate was compared between the groups using stratified Fisher's exact test.

Study EGF100151 enrolled its first patient in March of 2004, had one interim data analysis on November 15 of 2005, and last patient was enrolled on April 03 of 2006. A total of 399 patients were randomized; 324 of them were enrolled prior to the interim data analysis, and the rest of 75 patients were enrolled between the date of interim analysis and the date the sponsor stopped further enrollment following the recommendation from the Independent Data Monitoring Committee (IDMC).

### Statistical Issues:

Major statistical issues for Study EGF100151:

- 1) Prior to initiation of the study, there was a question on choosing the time to progression versus progression free survival (PFS) as the primary efficacy endpoint. The primary endpoint for this study is defined as time to progression or death due to breast cancer (TTP), and is different from PFS which includes all cause deaths.
- 2) One interim analysis on TTP was pre-specified with 133 events (disease progression or breast cancer related death). The interim analysis cut-off date of 15 November of 2005 was set when there were 146 investigator-determined events observed. One hundred thirty three (133) of the first occurred events were in the interim TTP analysis as pre-specified; 114 of these events were later confirmed by independent reviews for analysis presented to IDMC.
- 3) Big differences were observed in assessment of time to progression and response rate by investigators (INV) and independent review committee (IRC). It is the sponsor's view that the differences were a result of different selection of organs/lesions and/or interpretation of data. However, this reviewer has a serious concern on the discrepancy between INV and IRC assessments of disease progression because:
  - The advantage of combination therapy over capecitabine monotherapy in terms of median TTP was shortened from 18.4 weeks at interim analysis to 9.2 weeks at updated analysis per IRC assessments (hazard ratio of 0.48 at interim versus 0.55 at updated analysis);
  - There existed a big discrepancy between IRC and INV assessments of TTP advantage, especially in the combination arm.

Since time to progression is the primary efficacy endpoint and the study was stopped before survival data were mature for evaluation, the quality of data on tumor assessments is essential for an efficacy claim.

- 4) The updated IRC data on all enrolled patients should be used over the IRC interim data because the updated data provide a better estimation of median TTP and hazard ratio. Since the discrepancy between the investigator-determined and independently-reviewed TTP assessments could not be well explained, both INV and IRC TTP results need to be considered. With these discrepancies, it is not possible to characterize the effect size accurately.
- 5) The submitted survival data are not mature for evaluation. As of 03 April 2006, there were 119 deaths occurred. The difference in median survival between the two treatment

arms was only 1 week (67.7 versus 66.6 weeks for combination arm vs. capecitabine alone arm; two-sided p-value: 0.177). The calculated number of deaths for survival analysis with an 80% power to detect a 30% increase in median survival time in patients received lapatinib plus capecitabine was 457.

- 6) Due to the small number of deaths from causes other than breast cancer, the results of TTP analyses are similar to those of PFS analyses.
- 7) Study protocol was amended in December of 2004 to include trastuzumab as a required prior therapy. The impact of this amendment on efficacy results on all enrolled patients is small because only 6 patients enrolled without prior trastuzumab therapy, and the percentage of patients without trastuzumab as a prior therapy is similar between the arms (2 and 4 for combination arm and capecitabine alone arm respectively).
- 8) Study results based on all enrolled patients suggest that the combination arm was superior to the capecitabine alone arm with respect to time to disease progression or death due to breast cancer. Subgroup analyses by age and race also support this finding.

**APPEARS THIS WAY  
ON ORIGINAL**

**Findings on Primary Outcome – Time to Progression or Death due to Breast Cancer:**

Summary results of TTP using the data available from the clinical update cut-off date of 03Apr2006 are presented in Table 1. A total of 184 TTP events were identified by blinded independent reviews in 399 randomized patients. The independently assessed median TTP in the lapatinib+capecitabine group was 27.1 weeks compared to 17.9 weeks in the capecitabine group. The comparison between the treatment groups in the independently assessed TTP resulted in a hazard ratio of 0.55 (95% CI: 0.41, 0.74; two-sided p=0.00012). Using the investigator assessment of tumor response, the median TTP in the lapatinib+capecitabine group was 23.9 weeks compared to 17.9 weeks in the capecitabine group with a hazard ratio of 0.69 (95% CI: 0.54, 0.89; two-sided p=0.00737).

**Table 1 Summary Results of Time to Progression or Breast Cancer Death (ITT Population, 03Apr06 Data Cut-Off)**

	N = 399			
	Independent Reviews		Investigators	
	L+C n = 198	C n = 201	L + C n = 198	C n = 201
# Events (%)	82 (41%)	102 (51%)	121 (61%)	126 (63%)
Progressed Disease	69	86	114	117
Breast Cancer Death	13	16	7	9
Other Death	0	5	2	5
Median TTP <sup>a</sup> (week)	27.1	17.9	23.9	17.9
Difference in median TTP (week)	9.2		6.0	
Hazard Ratio <sup>b</sup>	0.55 (0.41 – 0.74)		0.69 (0.54 – 0.89)	
p-value <sup>c</sup>	0.00012		0.00737	

<sup>a</sup> Kaplan-Meier Estimate for median TTP

<sup>b</sup> Hazard Ratio calculated based on Cox model adjusting for stage and site of disease

<sup>c</sup> Two-sided p-value from stratified log-rank test, stratified for stage and site of disease, for comparing L + C versus C alone

Note: L + C = Lapatinib + Capecitabine; C = Capecitabine

**APPEARS THIS WAY  
ON ORIGINAL**

## **2. INTRODUCTION**

### **2.1 Overview**

Breast cancer is the most common malignancy and the second most common cause of cancer-related death in Western European and North American women. It has been shown that breast cancer patients who over-express the ErbB2 oncogene are at a higher risk of disease progression and death. Therefore, many therapeutic strategies have been developed with the intention to block the ErbB2 signaling pathways as means to improve the treatment efficacy of hormonal and chemotherapy regimens.

Trastuzumab, a monoclonal antibody directed against the extracellular domain of ErbB2, is registered for use in first line ErbB2 positive metastatic breast cancer. There is however no approved therapy for patients whose tumors have progressed on trastuzumab. It is common clinical practice after progression on a trastuzumab regimen, to change the cytotoxic component of the regimen while maintaining the biologic component of trastuzumab. Anthracyclines are commonly administered in the adjuvant setting and are often only administered in the metastatic setting if they have not been administered in the adjuvant setting because of concerns regarding toxicity. Capecitabine as monotherapy is approved for treatment of metastatic breast cancer after failure of anthracycline-containing chemotherapy.

Study EGF100151 was conducted as the major registration study to explore whether concomitant inhibition of both ErbB1/ErbB2 pathways with lapatinib improves the clinical efficacy of capecitabine in women with advanced breast cancer.

#### **2.1.1 Background**

Small molecule ErbB TKI's (tyrosine kinase inhibitors) compete intracellularly with adenosine triphosphate (ATP) for its receptor binding site and inhibit the receptor kinase's activity. Per sponsor, lapatinib differs in enzyme inhibition kinetics from other TKIs in the clinic in that the latter are all rapidly reversible, whereas lapatinib has a much slower off-rate for both ErbB1 and ErbB2.

Capecitabine as monotherapy is approved for treatment of patients with metastatic breast cancer after failure of anthracyclines and taxanes. It is an oral drug with an acceptable safety profile. In the setting of ErbB2 positive metastatic breast cancer it is commonly used after anthracyclines, taxanes and trastuzumab and is considered by the sponsor as an appropriate agent for combination with lapatinib in this particular setting. A phase I study of the combination of lapatinib and capecitabine was completed and determined an optimally tolerated regimen (OTR) of lapatinib 1250mg/day continuously and capecitabine 2000mg/m<sup>2</sup> /day for 14 days on a 21-day cycle.

Study EGF100151 was designed as the registration trial to demonstrate that lapatinib in combination with capecitabine is superior to capecitabine alone for the treatment of patients with

advanced or metastatic breast cancer whose tumors over-express ErbB2 and who have received prior therapy including trastuzumab. The study had a special protocol assessment, and started its patient enrollment in March of 2004. Based on recommendations from sponsor-appointed independent data monitoring committee (IDMC), the study was stopped on 03 April 2006 for superiority. The sponsor has submitted data on patients enrolled up to 15 November 2005 the data cut-off for IDMC interim analysis, and data on patients enrolled up to 03 April 2006 the study stopped date for Study EGF100151 as well as data from two Phase II studies and safety database of more than 3000 patients as supportive evidence for this indication.

### 2.1.2 Clinical Studies

The sponsor submitted data and study reports on the following 3 clinical studies in breast cancer patients:

1. Study EGF100151: Phase III randomized multi-center, open-label trial comparing efficacy and safety between two treatment groups (lapatinib + capecitabine and placebo + capecitabine) in ErbB2 over-expressed advanced or metastatic breast cancer patients. Study participants were randomized on a 1:1 ratio to receive either 2500 mg/m<sup>2</sup>/day capecitabine for 14 days every 21 days or 2000 mg/m<sup>2</sup>/day capecitabine for 14 days every 21 days plus 1250 mg lapatinib once daily continuously. Patients were treated until disease progression or until unacceptable toxicity had occurred. Total n = 324 patients as of 15 November 2005 (interim analysis cut-off date) was enrolled and evaluated. The final number of enrolled patients is 399 as the study stopped on 03 April 2006. The primary endpoint was time to progression, defined as time from randomization to disease progression or death due to breast cancer.
2. Study EGF20002: A Phase II open-label, multi-center, single-arm study of lapatinib as a single agent therapy in patients with advanced or metastatic breast cancer who have progressed while receiving trastuzumab-containing regimens. A total of 78 patients self-administrated oral lapatinib at a dose of 1250 mg or 1500 mg once daily until disease progression or withdraw from the study. The primary endpoint for this Phase II study was tumor response rate.
3. Study EGF20008: A Phase II open-label, multi-center, single-arm study of lapatinib as a single agent therapy in patients with advanced or metastatic breast cancer who have progressed while receiving trastuzumab-containing regimens. Lapatinib 1500 mg administrated once daily to a total of 229 female patients with advanced or metastatic breast cancer and refractory to anthracycline-, taxane- and capecitabine-containing regimens. The primary endpoint of response rate was evaluated in two cohorts – Cohort A of 140 patients with ErbB2 over-expressing tumors, and Cohort B of 89 patients without ErbB2 over-expressing tumors.

Study EGF100151 is used as the basis for the statistical review and evaluation since it is the only controlled clinical trial pertinent to the indication. Both data on 324 patients as of interim analysis cut off and data on the total enrolled 399 patients are reviewed.

### 2.1.3 Major Statistical Issues

Major statistical issues for Study EGF100151:

- 1) Prior to initiation of the study, there was a question on choosing the time to progression versus progression free survival (PFS) as the primary efficacy endpoint. The primary endpoint for this study is defined as time to progression or death due to breast cancer (TTP), and is different from PFS which includes all cause deaths.
- 2) One interim analysis on TTP was pre-specified with 133 events (disease progression or breast cancer related death). The interim analysis cut-off date of 15 November of 2005 was set when there were 146 investigator-determined events observed. One hundred thirty three (133) of the first occurred events were in the interim TTP analysis as pre-specified; 114 of these events were later confirmed by independent reviews for analysis presented to IDMC.
- 3) Big differences were observed in assessment of time to progression and response rate by investigators (INV) and independent review committee (IRC). It is the sponsor's view that the differences were a result of different selection of organs/lesions and/or interpretation of data. However, this reviewer has a serious concern on the discrepancy between INV and IRC assessments of disease progression because:
  - a. The advantage of combination therapy over capecitabine monotherapy in terms of median TTP was shortened from 18.4 weeks at interim analysis to 9.2 weeks at updated analysis per IRC assessments (hazard ratio of 0.48 at interim versus 0.55 at updated analysis);
  - b. There existed a big discrepancy between IRC and INV assessments of TTP advantage, especially in the combination arm.Since time to progression is the primary efficacy endpoint and the study was stopped before survival data were mature for evaluation, the quality of data on tumor assessments is essential for an efficacy claim.
- 4) The updated IRC data on all enrolled patients should be used over the IRC interim data because the updated data provide a better estimation of median TTP and hazard ratio. Since the discrepancy between the investigator-determined and independently-reviewed TTP assessments could not be well explained, both INV and IRC TTP results need to be considered. With these discrepancies, it is not possible to characterize the effect size accurately.
- 5) The submitted survival data are not mature for evaluation. As of 03 April 2006, there were 119 deaths occurred. The difference in median survival between the two treatment arms was only 1 week (67.7 versus 66.6 weeks for combination arm vs. capecitabine alone arm; two-sided p-value: 0.177). The calculated number of deaths for survival analysis with an 80% power to detect a 30% increase in median survival time in patients received lapatinib plus capecitabine was 457.
- 6) Due to the small number of deaths from causes other than breast cancer, the results of TTP analyses are similar to those of PFS analyses.

- 7) Study protocol was amended in December of 2004 to include trastuzumab as a required prior therapy. The impact of this amendment on efficacy results on all enrolled patients is small because only 6 patients enrolled without prior trastuzumab therapy, and the percentage of patients without trastuzumab as a prior therapy is similar between the arms (2 and 4 for combination arm and capecitabine alone arm respectively).
- 8) Study results based on all enrolled patients suggest that the combination arm was superior to the capecitabine alone arm with respect to time to disease progression or death due to breast cancer. Subgroup analyses by age and race also support this finding.

## 2.2 Data Sources

Data used for this review are located on network with paths “\CDSESUB1\N22059\N\_000\2006-09-13\CRT\Datasets\egf100151” and “\CDSESUB1\N22059\N\_000\2006-10-04\CRT\Datasets\egf100151”. Data as of 15 November 2005 were submitted on September 13 of 2006, and data on all enrolled patients were submitted on October 04 of 2006.

## 3. STATISTICAL EVALUATION

### 3.1 Evaluation of Efficacy

Data from Study EGF100151 will be used as the basis for determining whether lapatinib has improved capecitabine’s activity for treating advanced or metastatic breast cancer patients. Patients enrolled in Study EGF100151 were randomly assigned to receive either 2500 mg/m<sup>2</sup>/day capecitabine for 14 days every 21 days or 2000 mg/m<sup>2</sup>/day capecitabine for 14 days every 21 days plus 1250 mg lapatinib once daily continuously. Treatment was administered until disease progression occurred or withdrawal from the study due to unacceptable toxicity or other reasons.

At the time of interim analysis (15 November 2005), 324 patients were enrolled; 183 patients in combination arm, and 161 patients were in the capecitabine alone arm. The IDMC reviewed the interim analysis in March 2006, and recommended discontinuing enrollment. The final number of 399 enrolled patients includes the 324 patients and 75 additional patients enrolled between the date of interim analysis and the date that study enrollment were stopped on 03 April 2006. For the 399 enrolled patients as of 03 April 2006, 198 were randomized to the combination arm, and 201 were in the capecitabine alone arm. Time to progression or death due to breast cancer (TTP) was the primary endpoint for comparing the treatment arms. Study secondary efficacy endpoints include overall survival (OS), progression-free survival (PFS), 6-month PFS, overall response rate (complete and partial responses), clinical benefit (complete response, partial response or stable disease for at least 6 months), time to response, and duration of response.

### Reviewer's Comment:

IDMC reviewed preliminary (un-cleaned) interim data on 20 March 2006, and recommended halting further enrollment into the study and that patients in the capecitabine group be informed of results and be given the opportunity to receive lapatinib+capecitabine. The sponsor terminated subject enrollment on 03 April 2006.

#### **3.1.1 Study EGF100151**

Study EGF100151 is a randomized multi-center, open-label study in patients with advanced or metastatic breast cancer. The study was designed to see if lapatinib in combination with capecitabine is superior to capecitabine alone for treating metastatic breast cancer as assessed by time to progression or death due to breast cancer (TTP) as the primary endpoint, and by overall survival, progression-free survival, response rate, clinical benefit, time to response, and duration of response as the secondary endpoints. The first patient was randomized to the study on 29 March 2004, an interim analysis was conducted with a data cut-off date of 15 November 2005, and the study stopped enrollment on 03 April 2006 per IDMC recommendation. There were 324 patients accrued to the date of interim analysis, and there were a total of 399 patients enrolled to this study. This was a global study conducted at 141 centers. The majority of all available 399 patients were enrolled within the European Union (57%) and United States (19%); the rest of study participants came from Brazil, Argentina, Hong Kong, South Africa, and Australia.

##### **3.1.1.1 Study Design**

Study EGF100151 was a Phase III randomized, open-label, multi-center, parallel group study to evaluate and compare the treatment of lapatinib plus capecitabine versus capecitabine alone when administered to women with advanced or metastatic breast cancer who have received prior therapy, which included anthracyclines, taxanes and trastuzumab. Trastuzumab must have been received for advanced/metastatic disease, and may also have been given in an adjuvant setting.

Enrollment of 528 female patients (264 in each arm) was planned, and patients were randomized on a 1:1 ratio to one of two treatment arms. Patients received either 1250mg lapatinib daily continuously plus capecitabine 2000 mg/m<sup>2</sup>/day on Days 1-14, of a 21-day treatment cycle, or patients received capecitabine 2500 mg/m<sup>2</sup>/day alone on Days 1-14, of a 21-day treatment cycle. Treatment was administered until disease progression occurred or withdrawal from the study due to unacceptable toxicity or other reasons.

Clinical and laboratory parameters were assessed to evaluate disease response according to RECIST and toxicity of randomized therapy. Safety and efficacy assessments were generally performed every 6 weeks for the first 24 weeks, then every 12 weeks and at the end of treatment. Hematology and clinical chemistry assessments were conducted on all patients every 3 weeks and at the end of treatment. Patients withdrawn from investigational product without disease progression were assessed every 12 weeks until progression. Thereafter, patients were followed for survival at approximately 12-week intervals until death.

Reviewer's Comment:

It was recommended to the sponsor, as stated in the special protocol assessment letter, that a dose of capecitabine of 2000 mg/m<sup>2</sup>/day in both arms would be preferred because of concerns regarding toxicity observed at the 2500 mg/m<sup>2</sup>/day level.

### **3.1.1.2 Study Objectives**

#### **Primary Objective**

The primary objective of the study was to evaluate and compare time to progression (TTP) in patients with refractory advanced or metastatic breast cancer with ErbB2 overexpression, treated with lapatinib and capecitabine versus capecitabine alone.

#### **Secondary Objectives**

To evaluate and compare the two treatment arms with respect to:

- Overall survival
- Progression-free survival
- 6-month progression-free survival
- Overall response rate (complete and partial responses)
- Clinical benefit (complete response, partial response or stable disease for at least 6 months)
- Time to response
- Duration of response
- Treatment associated toxicity

### **3.1.1.3 Definition of Efficacy 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 radiologic imaging 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 - the time from randomization until death due to any cause
- Progression-free survival - the time from randomization until the first documented sign of disease progression or death due to any cause
- Six-month progression-free survival - the percentage of surviving patients who were progression-free six months after the date of randomization

- Overall tumor response rate - the percentage of patients achieving either a complete tumor response (CR) or a partial tumor response (PR)
- Clinical benefit - the percentage of patients with evidence of CR or PR or stable disease (SD) for at least 6 months
- Time to response - the time from randomization until first documented evidence of CR or PR (whichever status is recorded first)
- Duration of response – calculated in the subset of patients 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

#### **3.1.1.4 Statistical Analyses**

##### **Data Analysis Methods**

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. Patients withdrawn from study who have not progressed were to be assessed every 12 weeks until progression and then followed for survival.

Stratified log-rank test, stratified for stage and site of disease, was used to compare treatment arms in time-to-event endpoints including time to progression, overall survival, and progression free survival. In some cases where the oncologist may have indicated progression prior to the local radiologist, the date of the oncologist's progression was used in the analysis for time to progression and progression free survival. The time to event was censored at the time of last contact for overall survival if patient didn't die at the time of data cut-off. For calculating time to progression or progression free survival, the time was censored at the either date of the last independently reviewed radiological scan or the date of initiation of anti-cancer therapy whichever occurred first if the patient had neither progressed nor died, or at the date of randomization if the patient had only a baseline visit or did not have a date of independently reviewed radiological scan that was no later than the date of initiation of anti-cancer therapy.

Overall response rate was defined as the percentage of patients achieving either a complete response (CR) or partial response (PR). Clinical benefit response rate was defined as the percentage of patients with complete or partial tumor response or stable disease for at least 6 months. Patients with unknown or missing response were treated as non-responders. Overall and clinical benefit response rates were compared between treatment arms using stratified Fisher's exact test. Zelen's test for homogeneity of the odds ratios across all strata was performed as a measure of validation. An exact confidence interval for the assumed common odds ratio was calculated.

Duration of response was calculated in patients who achieved CR or PR as the time from first documented evidence of PR or CR until the first documented sign of either disease progression or death due to breast cancer. No formal comparisons between treatment groups were undertaken for this endpoint in the subgroup of responders.

As a sensitivity analysis, the analysis of TTP was repeated with all deaths (whether due to breast cancer or not) without prior progression, regarded as competing risks. In addition, progression-free survival was analyzed using the method of interval-censoring in consideration that the disease progression was assessed periodically.

### **3.1.1.5 Analysis Populations**

The Intent-to-Treat (ITT) population was composed of all randomized patients and was used for the analysis of efficacy data.

The Safety population was composed of all randomized patients who received at least one dose of randomized therapy and was based on the actual treatment received, if this differed from that to which the subject was randomized. This population was used for the analysis of safety data.

The Per-Protocol (PP) population was composed of all randomized and treated patients who complied closely with the protocol. The PP population was used to provide a supplementary analysis of time to progression only.

### **3.1.1.6 Sample Size Justification**

A total of 266 events (disease progression or deaths due to breast cancer) was determined as required for the final analysis of time to progression (TTP), defined as the time from randomization to disease progression or death due to breast cancer, to provide a 90% power in detecting a 50% increase from 3 months to 4.5 months (a hazard ratio of 0.667) in median TTP in patients who received lapatinib plus capecitabine with a one-sided Type I error of 0.025. For the sample size calculation, the distribution of time to progression was assumed to be exponential, and the accrual was assumed to be uniform with an average accrual rate at 22 patients per month.

A final enrollment of 528 was determined to have at least 457 deaths for the analysis of overall survival to have an 80% chance of successfully detecting a 30% increase in median survival time in patients who received lapatinib plus capecitabine, based on median survival times of 8 and 10.4 months in the capecitabine and lapatinib plus capecitabine arms, respectively.

#### **Reviewer's Comments:**

1. A comment was made by an external FDA consultant that a 6-week increase in TTP in the refractory metastatic setting would be considered a very low bar for approval.
2. The study protocol was amended in December of 2004 to increase the sample size from 372 patients as required for TTP analyses to achieve 266 events to a maximum of 528 patients for 457 deaths required for survival analysis (Protocol Amendment 5) in response to the Agency's recommendation to power up the study for survival evaluation.

### 3.1.1.7 Interim Analysis

For the primary endpoint of time to progression (TTP), there were a maximum of two analyses planned, to occur at approximately equally spaced numbers of events: 133 and 266 investigator-determined events. O'Brien-Fleming stopping boundaries with one-sided 2.5% significance level were used to reject the null hypothesis,  $H_0: \lambda \geq 1$ , or to reject it in favor of the alternative hypothesis,  $H_A: \lambda < 1$ , where  $\lambda$  was the hazard ratio for TTP: lapatinib+capecitabine versus capecitabine alone.

An IDMC was convened to review accumulating safety and efficacy (time to progression) data and to provide an opportunity to terminate the study early if:

- there were concerns regarding safety;
- there was strong evidence of superior efficacy of lapatinib plus capecitabine; or
- there was strong evidence that lapatinib plus capecitabine would fail to show superiority if the study was allowed to run to its planned completion.

One interim analysis was performed after 146 investigator-identified events (disease progression or death due to breast cancer prior to progression) were observed with a data cut-off date of 15 November 2005. One hundred and thirty three (133) of first occurred events went into the interim analysis as pre-specified; 114 of these events were identified by independent reviews. Based on 114 events, it was determined that O'Brien-Fleming futility stopping boundaries were crossed if stratified log-rank test gave a one-sided p-value  $\geq 0.4516$ , and the efficacy stopping boundaries were crossed if the log-rank test resulted in a one-sided p-value  $\leq 0.0014$ . On 20 March 2006, the IDMC recommended terminate the study for efficacy. The sponsor stopped enrollment on 03 April 2006, and allowed patients in the capecitabine alone arm to transfer to the lapatinib+capecitabine arm.

#### Reviewer's Comments:

1. The option given to IDMC to recommend stopping the study early for superiority does not adhere to the final protocol. In the final protocol, it states "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. If this second analysis of TTP provides support for the superiority of lapatinib plus capecitabine, then the study will continue to recruit approximately 528 patients. When 457 deaths have been observed, an additional analysis of the secondary endpoint of overall survival will be performed on the mature survival data."
2. Because fewer events were identified than pre-specified required number of events, the p-values for crossing stopping boundaries were re-calculated.
3. For data on patients enrolled up to 15 November 2005, the following changes were made after the IDMC review as a result of sponsor's data cleaning effort:
  - a. Seven additional events were identified; four in the lapatinib+capecitabine arm, and three in the capecitabine alone arm. One of these events was due to error in

CRF, and the other six events were missed because investigator's signature date on these records was after 15 November 2005.

- b. Three additional patients were included in the lapatinib+capecitabine arm. These patients were randomized prior to 15 November 2005, but their CRFs were not available for data entry until after the database was frozen for the IDMC analysis.
4. The sponsor has submitted the validated data for review. Datasets specifically used to generate data for the IDMC have not been provided to the FDA.
5. A total of 399 patients were enrolled in the study as of 03 April 2006 when the study stopped its enrollment. The final database recorded 119 deaths; 55 deaths in the lapatinib plus capecitabine group, and 64 deaths in the capecitabine alone group. The log-rank test was not able to declare a difference in median overall survival of 67.7 weeks versus 66.6 weeks as statistically significant based on the survival data collected this far (refer to section 3.1.1.8.3.2 for results on overall survival).

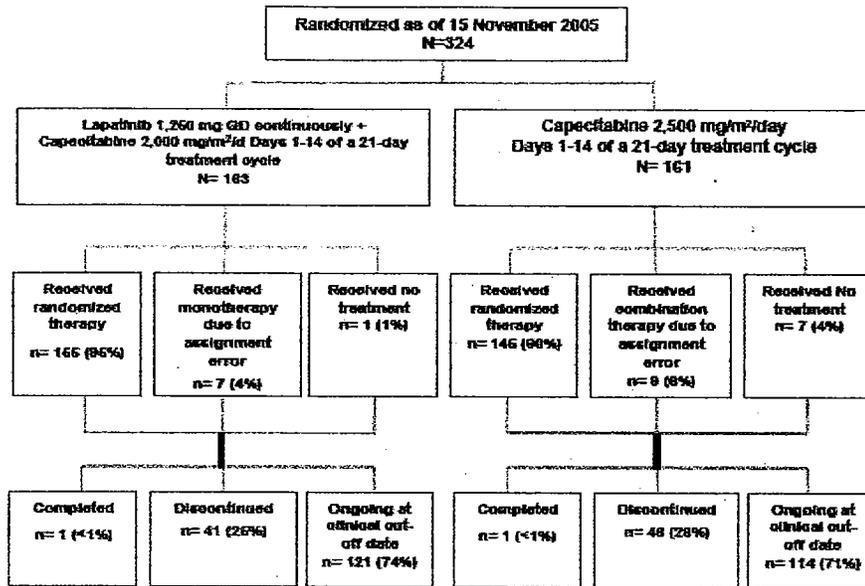
### **3.1.1.8 Efficacy Results and Conclusions**

#### **3.1.1.8.1 Disposition of Patients**

A total of 324 female patients with advanced or metastatic breast cancer were enrolled in the study up to 15 November 2005 (Figure 1). As of the data cut-off date, the majority of patients (73%) were still continuing in the study (either on treatment or being followed up for survival). The reason for discontinuation include death: 20% versus 21%; consent withdrawn: 2% versus 6%; and lost to follow-up: 2% versus 0% for combination arm versus capecitabine alone arm, respectively. For data up to the final enrollment, a total of 399 female patients with advanced or metastatic breast cancer were enrolled in the study (Figure 2). At the time enrollment was halted, the majority of patients (63%) were still on study with the reason for discontinuation to be death: 24% versus 29%; consent withdrawn: 2% versus 4%; and lost to follow-up: 3% versus 1% for combination arm versus capecitabine alone arm, respectively.

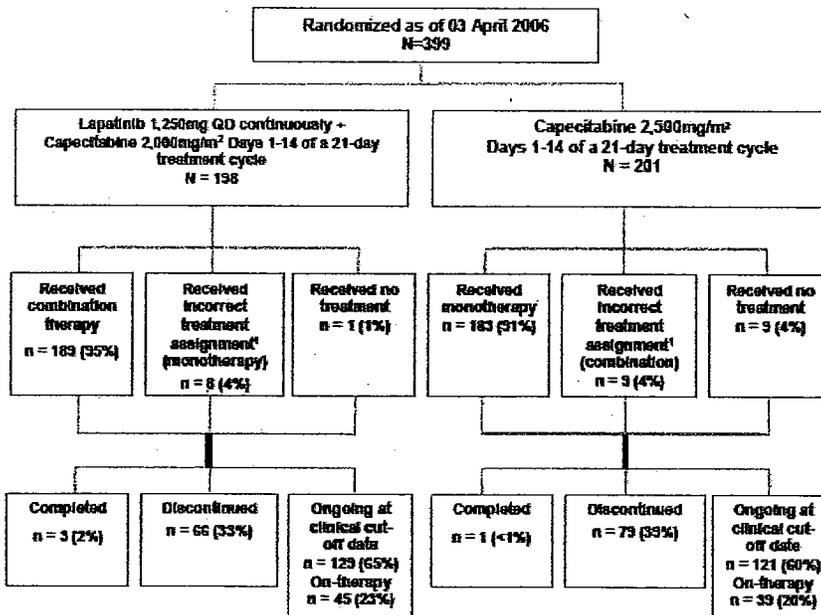
**APPEARS THIS WAY  
ON ORIGINAL**

**Figure 1 Subject Disposition (ITT Population, Data up to November 15, 2005) \***



\* Source: Figure 1 of study report per data up to November 15, 2005

**Figure 2 Subject Disposition (ITT Population, Data up to April 03, 2006) \*\***



\*\* Source: Figure 1 of study report per data up to April 03, 2006

The ITT population included all randomized patients, the safety population included all randomized patients 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 PP population included all the patients in the ITT population who had no major protocol violations. As shown in Table 2, a lower percentage of patients from capecitabine alone arm in the safety population compared to the combination arm. This was due to consent withdrawn from these patients for not receiving lapatinib. There was over 10% of randomized patients not in the PP population for reasons that they did not receive prior regimens of anthracycline or taxane or trastuzumab, or they received incorrect treatment, or they received no study medication.

**Table 2 Summary of Analysis Populations**

	Data per 15Nov2005 Cut-off			Data per 03Apr2006 Cut-off		
	L + C (N=163) n (%)	C (N=161) n (%)	Total (N=324) n (%)	L + C (N=198) n (%)	C (N=201) n (%)	Total (N=399) n (%)
ITT Population	163 (100)	161 (100)	324 (100)	198 (100)	201 (100)	399 (100)
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)

Note: L + C = Lapatinib+Capecitabine; C = Capecitabine alone

Reviewer's Comment:

Based on data as of 03Apr2006 cut-off, the two treatment arms have similar distributions with respect to reason for protocol violations except that the capecitabine alone arm has a higher percent of patients who did not receive any study medication due to consent withdrawal (4% versus <1% in combination arm). A total of 20 patients did not receive required prior regimens, and there were 17 patients who received medication different from randomized as a result of operational problems.

**3.1.1.8.2 Demographics and Other Baseline Characteristics**

The two treatment arms are similar with respect to demographics and baseline disease characteristics. Patients enrolled up to November 15 of 2005 and up to April 03 of 2006 have similar demographics and baseline characteristics distributions indicating no major differences between the patients enrolled before and patients enrolled after the interim data analysis cut-off date.

**Table 3 Summary of Demographics and Baseline Characteristics (ITT Population)**

	Patients enrolled as 15Nov2005			Patients enrolled as 03Apr2006		
	Group 1 [1] N=163	Group 2 [1] N=161	Total N=324	Group 1 [1] N=198	Group 2 [1] N=201	Total N=399
<b>Age, years</b>						
Mean (SD)	53.3 (10.72)	51.6 (10.53)	52.5 (10.64)	53.6 (10.54)	51.5 (10.34)	52.5 (10.48)
Median (min, max)	54.0 (26, 80)	51.0 (28, 83)	52.0 (26, 83)	54 (26, 80)	51 (28, 83)	53 (26, 83)
<b>Age group, n (%)</b>						
<65 years	138 (85)	142 (88)	280 (86)	165 (83)	177 (88)	342 (86)
>=65 years	25 (15)	19 (12)	44 (14)	33 (17)	24 (12)	57 (14)
<b>Race, n (%)</b>						
White	146 (90)	144 (89)	290 (90)	181 (91)	181 (90)	362 (91)
Asian	6 (4)	6 (4)	12 (4)	6 (3)	8 (4)	14 (4)
Hispanic	4 (2)	6 (4)	10 (3)	4 (2)	6 (3)	10 (3)
Black	5 (3)	2 (1)	7 (2)	5 (3)	3 (1)	8 (2)
Other	2 (1)	3 (2)	5 (2)	2 (1)	3 (1)	5 (1)
<b>Baseline disease stage</b>						
Stage IV – visceral	116 (71)	118 (73)	234 (72)	148 (75)	158 (79)	306 (77)
Stage IV – non-visceral	40 (25)	36 (22)	76 (23)	43 (22)	35 (17)	78 (20)
Stage IIIb or IIIc with T4 lesion	7 (4)	7 (4)	14 (4)	7 (4)	8 (4)	15 (4)
<b>Number of metastatic sites</b>						
>=3	79 (48)	80 (50)	159 (49)	98 (49)	96 (48)	194 (49)
2	53 (33)	46 (29)	99 (31)	61 (31)	61 (30)	122 (31)
1	31 (19)	34 (21)	65 (20)	39 (20)	44 (22)	83 (21)
0	0 (0)	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
<b>Weeks since last trastuzumab administrated</b>						
< 6 weeks	83 (53)	76 (49)	159 (49)	98 (50)	98 (50)	196 (49)
6-12 weeks	28 (18)	35 (22)	63 (19)	37 (19)	38 (19)	75 (19)
>12 weeks	46 (29)	43 (28)	89 (27)	61 (31)	58 (29)	119 (30)
Missing	0 (0)	2 (1)	2 (1)	0 (0)	3 (2)	3 (1)

[1] Group 1 = Lapatinib + Capecitabine; Group 2 = Capecitabine alone

### 3.1.1.8.3 Efficacy Results

#### 3.1.1.8.3.1 Time to Progression

The time to progression is defined as the time from randomization to disease progression or death due to breast cancer.

### 3.1.1.8.3.1.1 Results reviewed by Independent Data Monitoring Committee

Summarized in Table 4 is the analysis of independently assessed TTP as presented to Study EGF100151 Independent Data Monitoring Committee (IDMC) meeting on 20 March 2006. The difference between the treatment groups for independently assessed TTP was highly statistically significant with a hazard ratio of 0.51 (95% CI: 0.35, 0.74; two-sided p-value=0.00032). The independently assessed median TTP in the lapatinib+capecitabine group was 36.9 weeks compared to 19.7 weeks in the capecitabine group. The superiority boundary of 2-sided p-value = 0.0028 for comparing median TTP between treatment groups based on 114 events was crossed, and IDMC recommended to halt further enrollment into the study based on the presented results from 321 patients.

**Table 4 Summary of Time to Progression by Independent Review as Presented to the IDMC (ITT Population) \***

	<b>Lapatinib+ Capecitabine N=160</b>	<b>Capecitabine N=161</b>
<b>Progression and death, n (%)</b>		
Progressed or died due to breast cancer	45 (28)	69 (43)
Died due to cause other than breast cancer	0	4 (2)
Censored, follow-up ended	13 (8)	15 (9)
Censored, follow-up ongoing	102 (64)	73 (45)
<b>Cumulative incidence estimate of TTP, weeks</b>		
1 <sup>st</sup> Quartile	18.7	9.9
Median	36.9	19.7
3 <sup>rd</sup> Quartile	49.4	37.4
<b>Hazard ratio</b>		
Estimate, [95% CI] <sup>1</sup>	0.51 [0.35, 0.74]	
Log-rank p-value <sup>2</sup>	0.00032	

Data Source: Table 7.27

1. Hazard ratio of, <1 indicates a lower risk with lapatinib+capecitabine compared to capecitabine.
2. Two sided stratified log-rank test stratifying for stage of disease and site of disease at screening.

\* Source: Table 17 of study report based on data up to November 15, 2005

The IDMC was also presented with the summary results of investigator assessed TTP as in Table 5. Using investigator assessment of tumor response, the median TTP in the lapatinib plus capecitabine group was 25.3 weeks compared to 18.9 weeks in the capecitabine alone group; hazard ratio of 0.63 (95% CI: 0.44, 0.89; p-value= 0.007).

**Table 5 Summary of Time to Progression by Investigator Assessment as Presented to the IDMC (ITT Population) \***

	<b>Lapatinib+ Capecitabine N=160</b>	<b>Capecitabine N=161</b>
<b>Progression and death, n (%)</b>		
Progressed or died due to breast cancer	59 (37)	74 (46)
Died due to cause other than breast cancer	1 (<1)	4 (2)
Censored, follow-up ended	10 (6)	12 (7)
Censored, follow-up ongoing	90 (56)	71 (44)
<b>Cumulative incidence estimate of TTP, weeks</b>		
1 <sup>st</sup> Quartile	14.1	8.4
Median	25.3	18.9
3 <sup>rd</sup> Quartile	51.6	37.4
<b>Hazard ratio</b>		
Estimate, [95% CI] <sup>1</sup>	0.63 [0.44, 0.89]	
Log-rank p-value <sup>2</sup>	0.007	

Data Source: Table 7.28

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: Table 18 of study report based on data up to November 15, 2005

Reviewer's Comments:

1. The data used for IDMC review were not submitted as part of the NDA application.
2. The independent review committee identified fewer events than was pre-specified for the interim analysis; 114 events compared to desired 133 events. As a result, O'Brien-Fleming boundaries were re-calculated based on 114 events and it was determined that the superiority boundary for 114 events was crossed if the log-rank test resulted in a one-sided p-value  $\leq$  0.0014 (or equivalently, a two-sided p-value  $\leq$  0.0028).

**3.1.1.8.3.1.2 Results based on data submitted to the Agency**

Data submitted to this NDA include sponsor validated data on 324 patients enrolled prior to the interim analysis cut-off date 15 November 2005, and data on all enrolled 399 study participants randomized before study enrollment terminated on 03 April 2006.

Presented on the left side of Table 6 are results of TTP using sponsor validated data on all randomized patients prior to the data cut-off date of 15 November 2005. A total of 121 TTP events were identified by independent review committee (IRC) in 324 patients randomized. The

hazard ratio for comparing lapatinib + capecitabine versus capecitabine alone was 0.48 (95% CI: 0.33, 0.70). The independently assessed median TTP in the lapatinib+capecitabine group was 36.7 weeks compared to 18.3 weeks in the capecitabine group. The difference between the treatment groups in the independently assessed TTP was statistically significant with a two-sided p-value of 0.00008 considering the O'Brien Fleming (Pamplona-Tsiatis implementation) boundary for 121 TTP events was  $p \leq 0.0038$  (two-sided). Using the investigator assessment, the median TTP in the lapatinib+capecitabine group was 25.9 weeks compared to 18.3 weeks in the capecitabine group; hazard ratio of 0.59 (95% CI: 0.42, 0.83; p-value = 0.00209).

Results of TTP using the data available from the data cut-off date of 03Apr2006 are presented on the right side of Table 6. A total of 184 TTP events were identified by blinded independent review in 399 randomized patients. The independently assessed median TTP in the lapatinib+capecitabine group was 27.1 weeks compared to 17.9 weeks in the capecitabine group. The comparison between the treatment groups in the independently assessed TTP resulted in a hazard ratio of 0.55 (95% CI: 0.41, 0.74; two-sided  $p=0.00012$ ). Using the investigator assessment of tumor response, the median TTP in the lapatinib+capecitabine group was 23.9 weeks compared to 17.9 weeks in the capecitabine group with a hazard ratio of 0.69 (95% CI: 0.54, 0.89; two-sided  $p=0.00737$ ).

**Table 6 Summary Results of Time to Progression (ITT Population)**

	15Nov05 N = 324				03Apr06 N = 399			
	IRC		INV		IRC		INV	
	L+C n = 163	C n = 161	L+C n = 163	C n = 161	L+C n = 198	C n = 201	L+C n = 193	C n = 201
# Events (%)	49 (30%)	72 (45%)	59 (36%)	74 (46%)	82 (41%)	102 (51%)	121 (61%)	126 (63%)
Progressed Disease	40	61	55	69	69	86	114	117
Breast Cancer death	9	11	4	5	13	16	7	9
Other death	0	4	2	4	0	5	2	5
Median TTP <sup>a</sup> (week)	36.7	18.3	25.9	18.3	27.1	17.9	23.9	17.9
Improvement in TTP (week)	18.4		7.6		9.2		6.0	
Hazard Ratio	0.48 (0.33 – 0.70)		0.59 (0.42 – 0.83)		0.55 (0.41 – 0.74)		0.69 (0.54 – 0.89)	
p-value <sup>b</sup>	0.00008		0.00209		0.00012		0.00737	

<sup>a</sup> Kaplan-Meier Estimate for median TTP

<sup>b</sup> Two-sided p-value from stratified log-rank test, stratified for stage and site of disease, for comparing L+C versus C  
Note: L+C = lapatinib+capecitabine; C = capecitabine

Reviewer's Comments / Results:

1. The difference between the IDMC reviewed and later validated TTP results as of data cut-off date of 15 November of 2005 was due to that more patients and more deaths were identified in the validated data. Sever more deaths were identified in the validated data than the IDMC reviewed data. As a result, O'Brien-Fleming boundaries for TTP analysis were re-calculated based on 121 events and it was determined that the superiority boundary for 121 events was crossed if the log-rank test resulted in a one-sided p-value  $\leq 0.0019$  (or two-sided p-value  $\leq 0.0038$ ). The newly identified 7 deaths in the validated data were equally distributed between the treatment arms; 4 deaths came from the lapatinib+capecitabine group, and the other 3 deaths came from the capecitabine alone group. The magnitude of hazard ratio with the 7 new events was close to the one presented to IDMC.
2. Seventy-five (75) patients were enrolled and randomized between the interim analysis cut-off date (15 November of 2005) and the final enrollment date (03 April of 2006). Thirty five and forty of these seventy five later enrolled patients were assigned to the lapatinib+capecitabine and capecitabine alone groups, respectively.
3. Based on the reviewer's calculation, the O'Brien-Fleming efficacy stopping boundary is crossed based on 184 IRC determined events if the 2-sided p-value from stratified log-rank test is  $\leq 0.014$ .
4. The median TTP represented in sponsor's study report is 19.1 and 18.9 weeks at interim analysis for IRC and INV assessments respectively, and is 18.6 and 18.3 weeks at updated analysis for IRC and INV evaluations respectively for capecitabine arm. The sponsor's median TTP results are based on cumulative incidence curves, which accounts for competing risks of death due to causes other than breast cancer. Since the number of deaths other than breast cancer is small, the difference between the Kaplan-Meier based median TTP and cumulative incidence curve based median TTP is small.
5. The reviewer has reported the hazard ratios based on Cox models to be consistent with reviews made in the Division. The hazard ratios reported in sponsor's study report were Pick estimators, which use observed events and do not make assumptions on proportionality of hazards.
6. The p-values from stratified log-rank tests as calculated by the reviewer are close to, but different from the ones presented in the sponsor's reports. This is because that the reviewer used software SAS version 9.1 with a new procedure option while the sponsor has used a different option in the older version of SAS for performing the stratified log-rank tests.

### **3.1.1.8.3.1.3 Investigator versus Independent Reviews and Interim versus Updated in TTP**

#### **Problems Identified**

Several problems are identified from the TTP results per data submitted to the Agency:

- (1) The advantage of combination therapy over capecitabine monotherapy in terms of median TTP was shortened from 18.4 weeks at interim analysis to 9.2 weeks (hazard ratio of 0.48 at interim versus 0.55 at updated analysis)
- (2) There existed a big discrepancy between IRC and INV assessments of TTP advantage, especially in the combination arm

#### **Initial Data Evaluations**

At initial data evaluations, the reviewer found the following data deficiency:

- (1) In 4 patients, TTP was decreased by IRC from interim to updated data
- (2) There was a good portion of patients without tumor assessments. The number of patients with baseline only or no scans: at interim, 50 (15%) by INV and 72 (22%) by IRC; at update, 49 (12%) by INV and 62 (16%) by IRC.
- (3) In 15 patients, the IRC recorded as breast cancer death versus INV recorded disease progression at an earlier time point. It was thought by the review team that the IRC may not have reviewed all available scans, and may not have information on any subsequent therapies one received following an investigator determined disease progression.

#### **Sponsor's Responses**

The Agency had communicated with the sponsor through several emails and telephone conferences about the data concerns. In their response documents, the sponsor presented the following results from their evaluations:

- (1) There were 8 patients with discordance in the IRC assessed progression date or censor date between the 15 November 2005 dataset and the 03 April 2006 dataset (Table 7).
- (2) The conditional probability of progression free for lapatinib/capecitabine at 26.7 weeks on study for the 15 November 2005 dataset is 0.5232. No events occurred in the next 10 weeks so that the conditional probability did not cross over 50% until Week 36.7 (probability of 0.4941). For the 03 April 2006 dataset, the conditional probability went from 0.5088 at week 26.7 to 0.4972 at Week 27.1. The median TTP in combination arm obtained from the interim and update datasets are different because of the 10 week period in the 15 November 2005 dataset in which no events took place.
- (3) The hazard ratio for combination arm versus capecitabine alone arm based on IRC TTP became stable after about Week 75 and is relatively constant around 0.5 to 0.6 (Figure 3).
- (4) Disease assessment intervals are similar between the two arms (Figure 4).

- (5) The overall TTP Kaplan Meier curves for the combination treatment group as assessed by the IRC are very similar (Figure 5). The median TTP for IRC is shorter in the April 3 dataset is only an isolated difference in the two curves. The median TTP for the combination as assessed by the investigators was similar between the two datasets.
- (6) The reasons for difference between IRC and Investigator assessments for the 03 April 2006 dataset were presented in EGF100151 study report. The sponsor claims the results indicate the differences were generally due to differences in interpretations and selection of lesions and not due to lack of information.

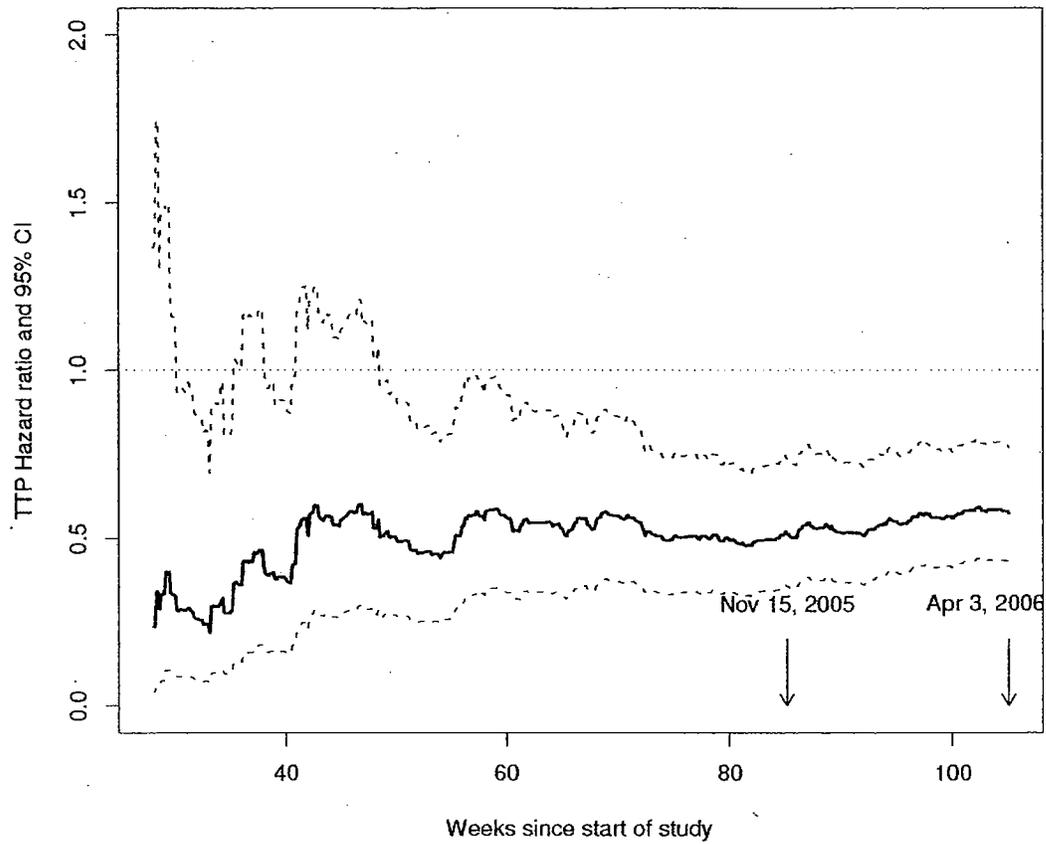
**Table 7 \* Listing of Patients with Different IRC Assessments in TTP Between 03 April 2006 and 15 November 2005**

Subject ID	Status 15Nov05	Status 03Apr06	Date of Assessment 15Nov05	Date of Assessment 03Apr06	Explanation of Difference in IRC Assessment
<b>Lapatinib plus Capecitabine Treatment Group</b>					
47	PD	PD	06Oct05	04Jul05	New on-study scans
708	PD	PD	24Mar05	03Jun05	More current baseline scans
1124	PD	Censored	27Jun05	01Feb06	More current baseline scans
<b>Capecitabine Treatment Group</b>					
691	PD	PD	06Jul05	22Aug05	More current baseline scans
709	PD	PD	06May05	10Mar05	new on-study scans
761	PD	Censored	10Nov05	18Aug05	received anticancer therapy
837	PD	Censored	11Apr05	11Apr05	More current baseline scans
1161	Censored	Censored	31Otc05	19Sep05	received anticancer therapy

\* Sponsor response document 'FDA response Tykerb 11 Jan Final.doc' Table 3.

**APPEARS THIS WAY  
ON ORIGINAL**

Figure 3 \* Hazard Ratio and 95% CI for IRC Time to Progression Over Time

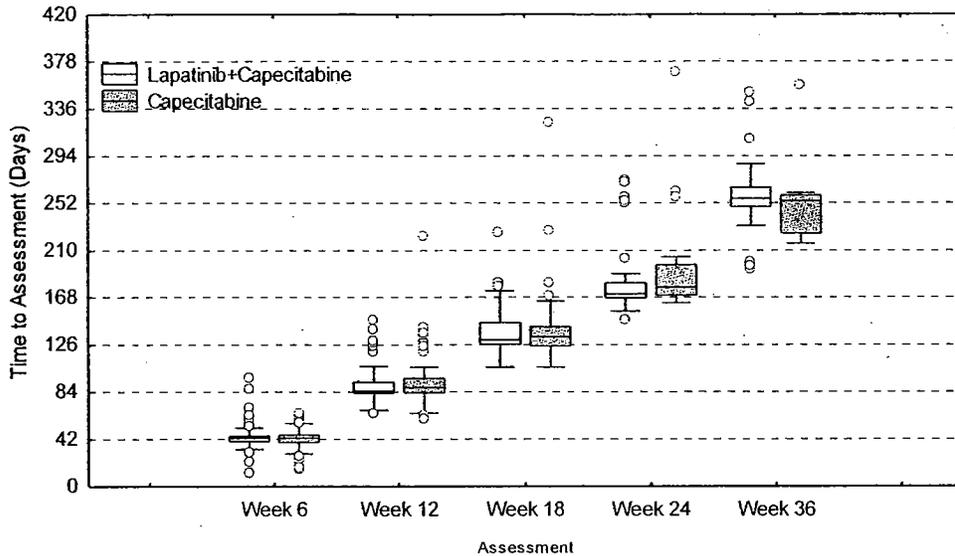


\* Sponsor response document 'FDA response Tykerb 11 Jan Final.doc' Figure 10.

Note: The hazard ratio over time plot was generated by the sponsor using R software (Survival Library)

**APPEARS THIS WAY  
ON ORIGINAL**

Figure 4 \* Compliance with Disease Assessment Times (15 November 2005)



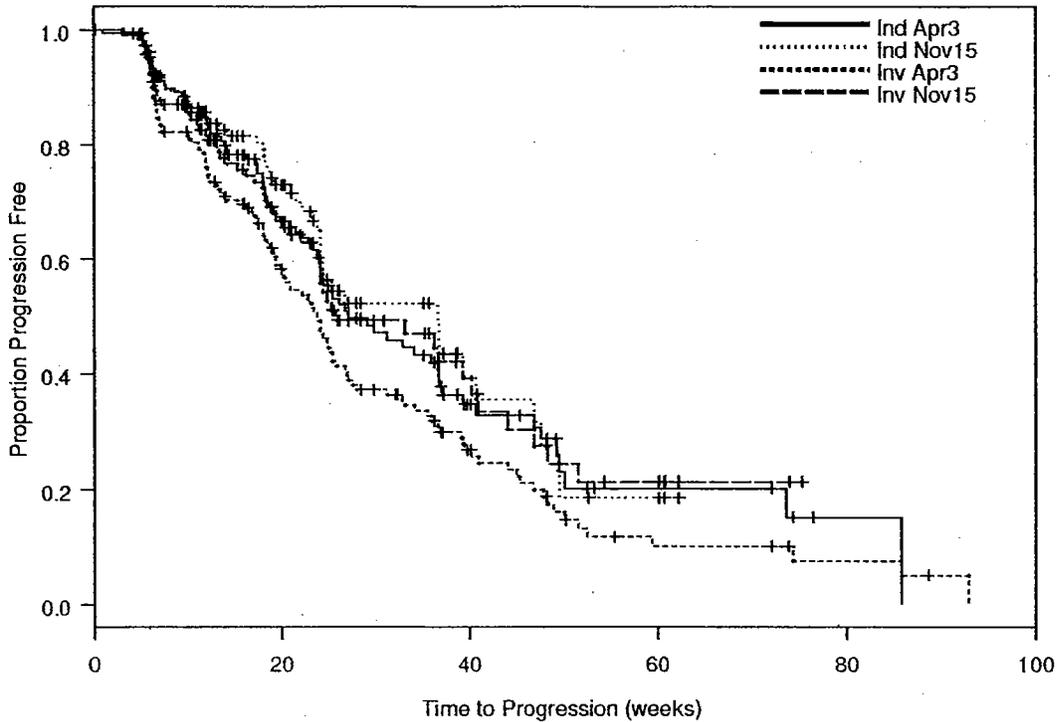
Subjects Assessed		Week 6	Week 12	Week 18	Week 24	Week 36
Lapatinib+Capecitabine		142	99	76	44	25
Capecitabine		130	83	53	27	14

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

\* Sponsor response document 'FDA response Tykerb 11 Jan Final.doc' Figure 11.

**APPEARS THIS WAY  
ON ORIGINAL**

Figure 5 \* IRC and Investigator Assessed Time to Progression for Lapatinib plus Capecitabine Treatment Arm



\* Sponsor response document 'FDA response Tykerb 11 Jan Final.doc' Figure 5.

*Reviewer's Comments and Results:*

- (1) Patients 47, 709, 1161, and 761 had IRC TTP decreased from interim to updated data.
- (2) The reviewer has calculated the proportion of event free at interim and update by IRC and INV (as shown below). No explanations were given by the sponsor on why long period with no-event was not observed as of 03 April 2006 dataset, and why this 10-week without an event by IRC at interim analysis was not seen by investigators.

**Table 8 Comparison of TTP Event Distribution**

Lapatinib +Capecitabine Arm					
IRC			INV		
Observed time (week)	Proportion event free At Interim	Proportion event free At Update	Observed time (week)	Proportion event free At Interim	Proportion event free At Update
26.714	0.523	0.509	23.429	0.615	0.508
27.143		0.497	23.857	0.601	
29.143		0.485	23.857	0.601	0.492
29.857		0.472	24.143		
31.286		0.459	24.143		
32.857		0.446	24.143	0.557	0.469
34.143		0.434	24.429	0.542	0.461
36.000		0.420	24.857	0.526	0.453
36.714	0.494	0.407	25.000		0.445
			25.286	0.510	0.438
			25.429		
			25.429		0.422
			25.857	0.493	0.414

- (3) Although the sponsor suggests the hazard ratio for IRC TTP got stabilized after Week 75 since start of study, the maximum IRC TTP event time observed for 15Nov2005 dataset was only 51 weeks. The 03Apr2006 updated dataset is better than the 15Nov2005 interim dataset for hazard ratio and point estimations with longer follow-up data.

**Further Agency Evaluations**

The Agency had further requested the CRFs on all events, and SAS data sets on all tumor assessments per INV and IRC at interim and separately at update. The requested items were received on January 11 of 2007.

Please refer to clinical review for the Agency’s further evaluations of CRFs.

***Additional TTP Analyses***

To explore the source and impact of such discrepancy in the magnitude of treatment advantage, the reviewer conducted the following additional analyses for IRC TTP:

1. Per-Protocol analysis – Limit the TTP analyses to patients without major protocol violations
2. Per treatment received analysis – Analyze the TTP data by treatment as received
3. TTP analyses based on revised data
  - a. Replace IRC TTP with INV TTP whenever IRC TTP > INV TTP
  - b. Replace IRC TTP with INV TTP when IRC TTP censored, but INV TTP event observed at a later date

4. Impact of the 75 enrolled patients – Results with the 324 early enrolled patients only
5. Stratified analyses by INV/IRC agreement status
6. TTP analysis excluding deaths due to breast cancer as events
7. Analysis of worst case scenario – Use minimum(IRC TTP, INV TTP) for the combination arm, and maximum(IRC TTP, INV TTP) for the capecitabine alone arm

## PP Results

There are 48 patients (15% of 324 patients) and 51 patients (13% of 399 patients) excluded from the Per-Protocol analyses of IRC TTP for protocol violation per data as of 15Nov2005 and data as 03Apr2006 respectively. The Per-Protocol analyses indicated a stringer treatment benefit in patients without a protocol violation compared to the ITT population with all randomized patients.

**Table 9 IRC TTP Results (Per Protocol Population)**

	15Nov05 N = 324		03Apr06 N = 399	
	L+C N = 146	C N = 130	L+C N = 180	C N = 168
# Events (%)	45 (31%)	61 (47%)	73 (41%)	88 (52%)
Kaplan-Meier estimates of TTP (weeks)				
25%-ile	18.7 (14.1 – 23.9)	8.6 (6.4 – 12.1)	18.0 (13.3 – 21.0)	8.3 (6.6 – 11.1)
50%-ile	36.9 (24.1 – 46.9)	17.6 (13.3 – 21.0)	27.1 (24.1 – 36.9)	17.6 (13.3 – 19.9)
75%-ile	49.4 (39.3 – NE)	36.0 (24.3 – 37.4)	49.4 (39.3 – 85.7)	30.9 (24.2 – 36.9)
Hazard Ratio [1]	0.430 (0.289 – 0.640)		0.480 (0.350 – 0.658)	
p-value from stratified [2] log-rank test	0.00001		<0.00001	

[1] HR calculated based on Cox model adjusting for strata (stage and site of disease)

[2] Stratified by strata (stage and site of disease)

NE = Not Estimable

## Per treatment received results

At interim analysis, 27 patients did not receive the regimen as randomized.

Received incorrect treatment: 16 (7 combination arm 9 capecitabine);

Received no treatment: 8 (1 combination arm, 7 capecitabine);

Received no anthracycline or no taxanes or no herceptin: 3 (1 received capecitabine, 2 no treatment)

At update analysis, 29 patients did not receive the regimen as randomized.

Received incorrect treatment: 17 (8 combination arm, 9 capecitabine);

Received no treatment: 10 (1 combination arm, 9 capecitabine);  
 Received no anthracycline or no taxanes or no herceptin: 2 (2 no treatment)

The IRC TTP results based on treatment as received are similar to the ones based on ITT population as randomized.

**Table 10 IRC TTP Results (Per Treatment Received)**

	15Nov05 N = 324		03Apr06 N = 399	
	L+C N = 164	C N = 153	L+C N = 198	C N = 192
# Events (%)	52 (32%)	69 (45%)	84 (42%)	100 (52%)
Kaplan-Meier estimates of TTP (weeks)				
25%-ile	19.1 (18.0 – 24.1)	8.7 (6.6 – 12.0)	18.0 (13.9 – 21.0)	8.6 (6.6 – 11.6)
50%-ile	36.9 (24.4 – 40.9)	17.6 (13.3 – 21.0)	29.1 (24.4 – 36.9)	17.6 (13.3 – 20.1)
75%-ile	49.3 (40.9 – NE)	36.0 (26.4 – NE)	49.3 (40.7 – 73.6)	36.0 (25.9 – 48.9)
Hazard Ratio [1]	0.419 (0.287 – 0.611)		0.523 (0.389 – 0.702)	
p-value from stratified [2] log-rank test	<0.00001		0.00002	

[1] HR calculated based on Cox model adjusting for strata (stage and site of disease)

[2] Stratified by strata (stage and site of disease)

NE = Not Estimable

**TTP analyses based on revised data**

- a. Replace IRC TTP with INV TTP whenever IRC TTP > INV TTP

Per protocol, the IRC should not have determined a later time to progression than the one determined by investigators. The revised TTP analysis is to correct the possible bias due to initiation of alternative chemotherapy (ACT) in situation that a subject had no IRC PD, but had death occurred after ACT. Number of data points affected is 37 for 15Nov2005 database and 56 for 03Apr06 database, respectively.

The IRC TTP results from the revised data are similar to the results from original data in terms of hazard ratios, but are better regarding the median TTP. The better median estimation is due to the changed event distribution with some IRC determined time to progression around the median been replaced by the investigator determined values.

**Table 11 Revised IRC TTP Results  
(Replace IRC TTP with INV TTP and recode IRC TTP as censored if IRC TTP > INV TTP)**

	15Nov05 N = 324		03Apr06 N = 399	
	L+C N = 163	C N = 161	L+C N = 198	C N = 201
# Events (%)	35	55	70	91
PD	33	50	65	82
BC death	2	5	5	9
Other Death	0	4	0	5
Kaplan-Meier estimates of TTP (weeks)				
25%-ile	18.7 (14.1 – 26.7)	11.6 (7.7 0 13.7)	17.4 (13.6 – 19.4)	9.9 (6.9 – 12.3)
50%-ile	40.7 (26.7 – NE)	19.9 (15.9 – 28.6)	32.9 (24.4 – 40.7)	18.6 (14.6 – 25.9)
75%-ile	NE (46.9 – NE)	37.4 (28.6 – 51.0)	85.7 (46.9 – 87.7)	36.9 (28.6 – 48.9)
Hazard Ratio [1]	0.456 (0.297 – 0.702)		0.555 (0.404 – 0.764)	
p-value from stratified [2] log-rank test	0.00027		0.00058	

[1] HR calculated based on Cox model adjusting for strata (stage and site of disease)

[2] Stratified by strata (stage and site of disease)

NE = Not Estimable

**b. Replace IRC TTP with INV TTP when IRC TTP censored but INV TTP event observed at a later date**

This analysis is attempted to correct possible bias due to incomplete information to the IRC. There were 11 patients (6 from combination arm, and 5 from the capecitabine arm) for 15Nov05 database and 21 patients (11 from combination and 10 from capecitabine) for 03Apr06 database recorded by IRC as censored, but had a later disease progression as determined by investigators.

The results as shown in Table 12 are close to the ones based on original IRC TTP values.

**Table 12 Revised IRC TTP Results  
(Replace IRC TTP with INV TTP and event status, if IRC TTP was censored  
but investigators had a later TTP event)**

	15Nov05 N = 324		03Apr06 N = 399	
	L+C N = 163	C N = 161	L+C N = 198	C N = 201
# Events (%)	55 (34%)	77 (48%)	93 (47%)	112 (56%)
Kaplan-Meier estimates of TTP (weeks)				
25%-ile	18.7 (14.1 – 24.1)	9.1 (7.4 – 12.1)	17.4 (12.3 – 19.4)	8.3 (6.7 – 11.6)
50%-ile	36.7 (24.4 – 40.7)	17.9 (13.7 – 21.0)	26.7 (24.1 – 36.0)	17.6 (13.3 – 19.9)
75%-ile	49.3 (40.3 – NE)	36.4 (26.4 – 43.4)	48.3 (39.3 – 73.6)	36.4 (25.9 – 38.0)
Hazard Ratio [1]	0.505 (0.355 – 0.719)		0.578 (0.437 – 0.764)	
p-value from stratified [2] log-rank test	0.00012		0.00017	

[1] HR calculated based on Cox model adjusting for strata (stage and site of disease)

[2] Stratified by strata (stage and site of disease)

NE = Not Estimable

#### Results with the 324 early enrolled patients only

To rule out the possibility that the later enrolled 75 patients could be different from the early enrolled patients regarding amount of information collected and important prognostic factors, the reviewer did a IRC TTP analysis using only the 324 patients enrolled prior to the 15Nov05 interim analysis cut-off. The result using data collected up to 03Apr06 on these 324 patients is close to the one based on data on all 399 enrolled patients.

**APPEARS THIS WAY  
ON ORIGINAL**

**Table 13 IRC TTP Results for the 324 patients who enrolled prior to 15Nov05**

	15Nov05 N = 324		03Apr06 N = 324	
	L+C N = 163	C N = 161	L+C N = 163	C N = 161
# Events (%)	49 (30%)	72 (45%)	75 (46%)	92 (57%)
PD	40	61	62	78
BC death	9	11	13	14
Other Death	0	4	0	5
Kaplan-Meier estimates of TTP (weeks)				
25%-ile	18.7 (14.1 – 24.1)	9.9 (7.4 – 12.4)	18.3 (14.1 – 22.3)	10.1 (7.6 – 12.1)
50%-ile	36.7 (24.1 – 46.9)	18.3 (13.7 – 24.3)	29.9 (24.4 – 36.9)	18.6 (14.3 – 24.3)
75%-ile	49.3 (40.7 – NE)	36.4 (26.4 – 43.4)	49.4 (40.1 – 85.7)	36.6 (26.4 – 43.4)
Hazard Ratio [1]	0.482 (0.334 – 0.697)		0.538 (0.395 – 0.733)	
p-value from stratified [2] log-rank test	0.00008		0.00013	

[1] HR calculated based on Cox model adjusting for strata (stage and site of disease)

[2] Stratified by strata (stage and site of disease)

NE = Not Estimable

### Results by IRC/INV agreement status

The IRC TTP results by IRC/INV agreement status are shown in the following table. If we were to limit the analysis to patients received complete agreement between IRC and investigators, the results are better than overall. The statistical significance is not achieved in the group of patients who had different time to progression as determined by IRC and investigators. However, the disagreement is not likely to bias the overall results since both IRC and INV had a similar conclusion for this group of patients.

**Table 14 TTP Results by IRC/INV Agreement Status  
(03Apr06 Database, ITT Population, N = 399)**

	Complete Agreement <sup>a</sup> (N = 211)		Disagreement <sup>b</sup> (N = 188)			
	L+C (n=96)	C (n=115)	IRC results		INV results	
	L+C (n=102)	C (n=86)	L+C (n=102)	C (n=86)	L+C (n=102)	C (n=86)
Event (%)	41 (43%)	59 (51%)	41 (40%)	43 (50%)	80 (78%)	67 (78%)
Kaplan-Meier Estimates of TTP (week)						
25%-ile	14.1	6.4	18.7	12.6	11.7	9.0
50%-ile (median)	24.1	13.3	29.9	25.9	23.4	19.1
75%-ile	50.0	19.9	49.4	40.9	39.4	38.0
Hazard Ratio [1]	0.441 (0.291 – 0.667)		0.713 (0.461 – 1.102)		0.975 (0.700 – 1.358)	
p-value from stratified [2] log-rank test	0.00007		0.12491		0.87971	

a Complete agreement = both event status (event or censored) and TTP are the same between IRC and INV TTP determination

b Disagreement = other than complete agreement

[1] HR estimated from Cox model with site and stage of disease as stratification factors

[2] Stratified by site and stage of disease

**TTP analysis excluding deaths due to breast cancer as events**

As a sensitivity analysis, the analysis of IRC TTP was repeated considering only disease progression as an event. The results are better in terms of median TTP as the event distribution is slightly different from the one of original values, but the magnitude of hazard ratios remained similar.

**Table 15 IRC TTP Results with only Disease Progression as an event  
(ITT Population)**

	15Nov05 N = 324		03Apr06 N = 399	
	IRC		IRC	
	L+C n = 163	C n = 161	L+C N = 198	C n = 201
# Events (%)	40 (24%)	61 (38%)	69 (35%)	86 (43%)
Median (weeks)	36.9	19.9	31.3	18.6
HR [1] (95% CI)	0.48 (0.32, 0.72)		0.54 (0.39, 0.74)	
Log-rank p-value [2]	0.00029		0.00025	

[1] HR estimated from Cox model with site and stage of disease as stratification factors

[2] Stratified by site and stage of disease

Note: L+C = lapatinib+capecitabine; C=capecitabine alone

### TTP analysis per worst case scenario

As the worst case scenario, the IRC TTP analysis was done letting the TTP=minimum(IRC TTP, INV TTP) for the combination arm, and TTP=maximum(IRC, INV TTP) for the capecitabine alone arm. The treatment benefit in terms of median TTP is down to only 2 weeks per data as of 03Apr06, and the hazard ratio is no longer statistically significant.

**Table 16 Exploratory TTP Analysis – Worst Case Scenario**  
**For L+C, use min(IRC TTP, INV TTP)**  
**For C, use max(IRC TTP, INV TTP)**  
**Event Determination based on method (IRC or INV) with the chosen TTP**

	15Nov05 N = 324		03Apr06 N = 399	
	L+C N = 163	C N = 161	L+C N = 198	C N = 201
# Events (%)	61 (37%)	77 (48%)	117 (59%)	123 (61%)
Kaplan-Meier estimates of TTP (weeks)				
25%-ile	13.0 (10.0 – 18.1)	8.6 (6.3 – 12.1)	11.9 (8.6 – 13.9)	7.7 (6.3 – 11.6)
50%-ile	24.1 (19.4 – 36.7)	19.7 (15.1 – 26.4)	20.4 (18.3 – 24.1)	18.3 (15.9 – 19.9)
75%-ile	46.9 (36.7 – NE)	37.4 (31.1 – 51.0)	36.9 (28.0 – 49.4)	36.6 (25.9 – 43.0)
Hazard Ratio [1]	0.751 (0.536 – 1.053)		0.832 (0.645 – 1.074)	
p-value from stratified [2] log-rank test	0.08175		0.22690	

[1] HR calculated based on Cox model adjusting for strata (stage and site of disease)

[2] Stratified by strata (stage and site of disease)

NE = Not Estimable

#### Reviewer's Comments:

1. All the additional analyses except the one for the worst case scenario indicate a treatment benefit for lapatinib+capecitabine versus capecitabine as a monotherapy.
2. Based on the data as submitted, the O'Brien-Fleming boundary was crossed based on the observed events indicates a high possibility of statistically significant treatment effect will be observed if the study is to continue to its final TTP analysis as pre-specified.

### 3.1.1.8.3.2 Overall Survival

At the time of the final enrollment date (03Apr2006), 55 patients (28%) in the lapatinib+capecitabine group and 64 patients (32%) in the capecitabine group had died (Table 17). The principal reason for death in both treatment groups was disease progression (27% versus 29% respectively).

The median survivals were similar between the two groups based on the updated data with a hazard ratio of 0.78 (95% CI: 0.55, 1.12; p-value=0.177).

**Table 17 Summary of Overall Survival (ITT Population) (03Apr2006 Cut-Off) \*\***

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

Data Source: Table 7.7 and Table 7.8

\*\* Source: Table 16 of study report based on data as of 03 April of 2006

Reviewer's Comment:

The submitted survival data were not sufficiently mature to make any conclusions on overall survival between the treatment groups. The calculated number of deaths for survival analysis with an 80% power to detect a 30% increase in median survival time in patients received lapatinib plus capecitabine was 457.

### 3.1.1.8.3.3 Progression Free Survival and 6-Month Progression Free Survival

Based on the updated data as of 03 April 2006 on all randomized patients, the independently assessed median time for progression-free survival (PFS) was 27.1 weeks in the lapatinib+capecitabine group and 17.6 weeks in the capecitabine group with a hazard ratio of 0.55 (95% CI: 0.41, 0.74; two-sided p=0.000033) (Table 18 and Figure 6).

Following the independent assessment of tumor response there was a 52% probability of patients remaining progression free at 6 months in the lapatinib+capecitabine group compared with a 33% probability in the capecitabine group.

**Table 18 Summary of Progression Free Survival (ITT Population) (03Apr2006 Cut-Off) \*\***

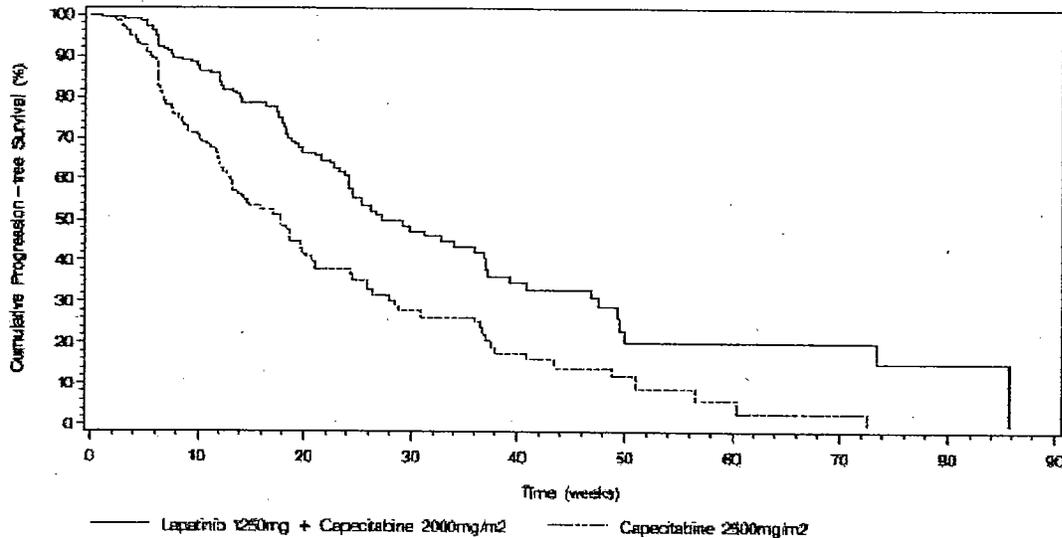
	Lapatinib+Capecitabine N=198	Capecitabine N=201
<b>Subject progression, n (%)</b>		
Progressed or died	82 (41)	107 (53)
Censored, follow-up ended	20 (10)	23 (11)
Censored, follow-up ongoing	96 (48)	71 (35)
<b>Kaplan-Meier estimate of PFS, weeks</b>		
1 <sup>st</sup> Quartile, [95% CI]	17.4 [13.6,19.9]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

Data Source: Table 7.9

\*\* Source: Table 17 of study report based on data as of 03 April 2006

**APPEARS THIS WAY  
ON ORIGINAL**

**Figure 6 Kaplan-Meier Estimates of Progression Free Survival (ITT Population) (03Apr2006 Cut-Off) \*\***



Reviewer's Comment:

The results on PFS are similar to the results of TTP because there were only 7 investigator-determined deaths not due to breast cancer, which is considered as an event for PFS analyses but not treated as an event for TTP analyses.

**3.1.1.8.3.4 Response Rate**

Based on the blinded independent review up to 03 April of 2006, the response rate (complete or partial response) was 24% in the lapatinib+capecitabine group versus 14% in the capecitabine group. The odds ratio was 1.9 (95% CI: 1.1, 3.4; two-sided p=0.017) (Table 19). The investigator assessment of response rate was 32% for the lapatinib+capecitabine group and 17% for the capecitabine group. This odds ratio was 2.2 (95% CI: 1.3, 3.6; two-sided p=0.002) (Table 20).

**Table 19 Summary of Independent Review Panel-Evaluated Response Rate (ITT Population) (03Apr2006 Cut-Off) \*\***

	Lapatinib+Capecitabine N=198	Capecitabine N=201
<b>Best Response, n (%)</b>		
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)
<b>Response rate (CR or PR)<sup>1</sup></b>		
Response rate % [95% CI]	23.7 [18.0,30.3]	13.9 [9.5,19.5]
<b>Difference in response rate (CR or PR)</b>		
Difference, % [95% CI]	9.8 [0.8,19.3]	
<b>Estimate of common odds ratio for tumor response estimate</b>		
Estimate [95% CI]	1.9 [1.1,3.4]	
Exact test two-sided p-value	0.017	

Data Source: Table 7.18

1. Subjects with unknown or missing responses were treated as non-responders.

\* Source: Table 18 of study report based on data as of 03 April of 2006

**Table 20 Summary of Investigator Assessment of Response Rate (ITT Population) (03Apr2006 Cut-Off) \*\***

	Lapatinib+Capecitabine N=198	Capecitabine N=201
<b>Best Response, n (%)</b>		
Complete response (CR)	5 (3)	1 (<1)
Partial response (PR)	58 (29)	34 (17)
Stable disease (SD)	61 (31)	65 (32)
Progressive disease (PD)	43 (22)	53 (26)
Unknown	31 (16)	48 (24)
<b>Response rate (CR or PR)</b>		
Response rate % [95% CI]	31.8 [25.4,38.8]	17.4 [12.4,23.4]
<b>Difference in response rate (CR or PR)</b>		
Difference, % [95% CI]	14.4 [4.9,24.0]	
<b>Estimate of common odds ratio for tumor response estimate</b>		
Estimate [95% CI]	2.2 [1.3,3.6]	
Two sided p-value	0.002	

Data Source: Table 7.21

1. Subjects with unknown or missing responses were treated as non-responders.

\* Source: Table 19 of study report based on data as of 03 April of 2006

#### **3.1.1.8.3.5 Clinical Benefit Response Rate (not considered for regulatory decision making)**

Based on updated data up to 03 April of 2006, the clinical benefit response rate in the lapatinib+capecitabine group was 29%, and was 17% in the capecitabine group (odds ratio: 2.0, 95% CI: 1.2, 3.3; two-sided p=0.008). This compares with the investigator-assessed clinical benefit response rate of 37% for patients in the lapatinib+capecitabine group, and a rate of 21% for patients in the capecitabine group.

#### **3.1.1.8.3.6 Duration of Response**

Duration of response was calculated in patients who had CR or PR 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. Based on data up to 03 April of 2006, the median duration of response was 32.1 weeks in the lapatinib+capecitabine group and 30.6 weeks in the capecitabine group.

#### **3.1.1.8.3.7 Other Efficacy Results**

##### **Analysis of Independent versus Investigator Assessed Response**

The sponsor has presented the following tables explaining the differences between the IRC and the investigator assessment of TTP in Study EGF100151. It is the sponsor's view that the differences were a result of different selection of organs/lesions and/or interpretation of data.

**APPEARS THIS WAY  
ON ORIGINAL**

**Table 21 Summary of Comparison of Investigator and IRC-evaluated Time to Progression \***

	Lapatinib+ Capecitabine N=163	Capecitabine N=161	Total N=324
<b>Progression by IRC</b>			
<b>N</b>	49	72	121
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%) <sup>1</sup>	19 (26%)	34 (28%)
<b>Censored by IRC</b>			
<b>N</b>	114	89	203
Complete Agreement with INV	60 (53%)	54 (61%) <sup>2</sup>	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%)

Data source: Table 7.36

INV=investigator

1. Includes 2 patients who died from causes other than breast cancer.

2. Includes 4 patients who died from causes other than breast cancer.

\* Source: Table 23 of study report based on data as of November 15 of 2005

**APPEARS THIS WAY  
ON ORIGINAL**

**Table 22 Overall Summary of Reasons for Differences Between IRC and Investigator Assessment of Progression \***

	Lapatinib+ Capecitabine	Capecitabine	Total
<b>Total PD Events Considered Different for TTP Analysis</b>	58	55	113
<b>Total PD Events Observed That Were Different</b>	55 <sup>1</sup>	50 <sup>2</sup>	105
Interpretation of Data only	23	21	44
Different Selection of Organ/ Lesions only	10	12	22
Both Interpretation and Selection	15	12	27
Missing Data (baseline imaging, photos, clinical information)	7	5	12

Data Source: Attachment 4

1. Excludes the 3 patients where there was agreement on PD, however, for investigator analysis of TTP these occurred after the protocol defined number of events (133).
2. Excludes the 5 patients where there was agreement on PD, however, for investigator analysis of TTP these occurred after the protocol defined number of events (133).

\* Source: Table 24 of study report per data as of November 15 of 2005.

The sponsor also presented a summary of the independent and investigator assessments of the subject's response to treatment per data as of 15Nov2005. Overall 41% of patients in the lapatinib+capecitabine group and 49% of patients in the capecitabine group had the same assessment of tumor response from both the independent and investigator evaluations.

**APPEARS THIS WAY  
ON ORIGINAL**

**Table 23 Summary of Independent and Investigator Evaluated Best Response \***

Independent Review	Investigator Evaluation					
	CR	PR	SD	PD	nknown	Total
<b>Lapatinib+ Capecitabine N=163</b>						
CR	0	1	0	0	0	1
PR	0	28	5	2	0	35
SD	2	8	34	11	2	57
PD	0	2	4	5	5	16
Unknown	3	4	8	14	25	54
<b>Total</b>	<b>5</b>	<b>43</b>	<b>51</b>	<b>32</b>	<b>32</b>	<b>163</b>
<b>Capecitabine N=161</b>						
CR	0	0	0	0	0	0
PR	0	17	6	0	0	23
SD	0	7	37	3	1	48
PD	0	1	6	25	1	33
Unknown	0	2	4	12	39	57
<b>Total</b>	<b>0</b>	<b>27</b>	<b>53</b>	<b>40</b>	<b>41</b>	<b>161</b>

Data Source: Table 7.14

Source: Table 30 of study report per data as of November 15 of 2005.

### 3.1.1.8.4 Conclusions for Efficacy

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 trastuzumab. 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 a hazard ratio of 0.55 per independently reviewed assessments, and 23.9 weeks versus 17.9 weeks with a 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 a longer follow-up.

### 3.2 Evaluation of Safety

Please refer to Clinical Evaluations of this application for safety results and conclusions.

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race and Age

Study EGF100151 TTP results based on independent reviews by age (<65, 65+) and race (Caucasians vs. the others) are presented in Tables 24 and 25. The results indicate a treatment benefit across age groups. The treatment advantage in terms of median TTP is close between Caucasians and other races, but the statistical significance for a treatment benefit was achieved for non-Caucasians due to the small size of the group.

**Table 24 IRC TTP Results by age (ITT population, data as of 03Apr06)**

	< 65 years old N = 342		≥ 65 years old N = 57	
	L+C n = 165	C n = 177	L+C n = 33	C N = 24
# Events (%)	71 (43%)	91 (51%)	11 (33%)	11 (46%)
Kaplan-Meier estimates of TTP (weeks)				
25%-ile	18.0 (13.6 – 19.9)	9.1 (6.9 – 12.0)	17.4 (9.9 – 27.1)	9.1 (3.0 – 17.0)
50%-ile	29.1 (23.9 – 36.9)	18.3 (13.7 – 21.0)	26.7 (18.3 – NE)	17.0 (9.1 – 24.3)
75%-ile	49.4 (40.7 – 85.7)	36.6 (26.4 – 43.4)	34.1 (26.7 – NE)	24.3 (17.0 – 28.0)
p-value from stratified [1] log-rank test	0.00089		0.00652	

[1] Stratified by strata (stage and site of disease)

NE = Not Estimable

**APPEARS THIS WAY  
ON ORIGINAL**

**Table 25 IRC TTP Results by race (ITT population, data as of 03Apr06)**

	Caucasians N = 362		Others N = 37	
	L+C n = 181	C n = 181	L+C n = 17	C N = 20
# Events (%)	72 (40%)	89 (49%)	10 (59%)	13 (65%)
Kaplan-Meier estimates of TTP (weeks)				
25%-ile	18.0 (13.9 – 21.6)	9.9 (6.7 – 12.0)	11.1 (9.1 – 26.1)	6.1 (5.3 – 17.9)
50%-ile	29.1 (24.1 – 36.9)	18.3 (13.3 – 20.7)	26.1 (11.9 – 37.1)	17.9 (6.4 – 37.4)
75%-ile	49.4 (40.7 – 85.7)	36.0 (25.9 – 40.9)	37.1 (26.1 – 73.6)	37.4 (17.9 – 72.4)
p-value from stratified [1] log-rank test	0.00008		0.30878	

[1] Stratified by strata (stage and site of disease)

## 5. SUMMARY AND CONCLUSIONS

This is a NDA submission seeking approval of lapatinib 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 trastuzumab. Study EGF100151 was conducted as the Phase III trial intended for such indication.

Study EGF100151 is a Phase III randomized multi-center, open-label trial in ErbB2 over-expressed advanced or metastatic breast cancer patients. Study participants were randomized on a 1:1 ratio to receive either 2500 mg/m<sup>2</sup>/day capecitabine for 14 days every 21 days or 2000 mg/m<sup>2</sup>/day capecitabine for 14 days every 21 days plus 1250 mg lapatinib once daily continuously. Patients were treated until disease progression or until unacceptable toxicity had occurred. Safety and efficacy assessments were performed every 6 weeks for the first 24 weeks, then every 12 weeks and at the end of treatment. The primary efficacy endpoint was time to progression, defined as time from randomization to disease progression or death due to breast cancer. Secondary efficacy endpoints include progression free survival, overall survival, response rate, clinical benefit, and duration of response. The two treatment groups were compared in terms of time to event endpoints including time to progression, progression free survival, and overall survival using log-rank test stratified for stage and site of disease. Overall and clinical benefit response rates were compared between the groups using stratified Fisher's exact test.

Study EGF100151 enrolled its first patient in March of 2004, had one interim data analysis on November 15 of 2005, and had its final patient enrollment on April 03 of 2006. A total of 399 patients were randomized; 324 of them were enrolled prior to the interim data analysis, and the rest of 75 patients were enrolled between the date of interim analysis and the date the sponsor stopped further enrollment following the recommendation from the Independent Data Monitoring Committee (IDMC).

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 per independently reviewed assessments, and 23.9 weeks versus 17.9 weeks 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.

## 5.1 Statistical Issues and Collective Evidence

Major statistical issues for Study EGF100151:

- 1) Prior to initiation of the study, there was a question on choosing the time to progression versus progression free survival (PFS) as the primary efficacy endpoint. The primary endpoint for this study is defined as time to progression or death due to breast cancer (TTP), and is different from PFS which includes all cause deaths.
- 2) One interim analysis on TTP was pre-specified with 133 events (disease progression or breast cancer related death). The interim analysis cut-off date of 15 November of 2005 was set when there were 146 investigator-determined events observed. One hundred thirty three (133) of the first occurred events were in the interim TTP analysis as pre-specified; 114 of these events were later confirmed by independent reviews for analysis presented to IDMC.
- 3) Big differences were observed in assessment of time to progression and response rate by investigators (INV) and independent review committee (IRC). It is the sponsor's view that the differences were a result of different selection of organs/lesions and/or interpretation of data. However, this reviewer has a serious concern on the discrepancy between INV and IRC assessments of disease progression because:
  - a. The advantage of combination therapy over capecitabine monotherapy in terms of median TTP was shortened from 18.4 weeks at interim analysis to 9.2 weeks at updated analysis per IRC assessments (hazard ratio of 0.48 at interim versus 0.55 at updated analysis);
  - b. There existed a big discrepancy between IRC and INV assessments of TTP advantage, especially in the combination arm.

Since time to progression is the primary efficacy endpoint and the study was stopped before survival data were mature for evaluation, the quality of data on tumor assessments is essential for an efficacy claim.

- 4) The updated IRC data on all enrolled patients should be used over the IRC interim data because the updated data provide a better estimation of median TTP and hazard ratio. Since the discrepancy between the investigator-determined and independently-reviewed TTP assessments could not be well explained, both INV and IRC TTP results need to be

considered. With these discrepancies, it is not possible to characterize the effect size accurately.

- 5) The submitted survival data are not mature for evaluation. As of 03 April 2006, there were 119 deaths occurred. The difference in median survival between the two treatment arms was only 1 week (67.7 versus 66.6 weeks for combination arm vs. capecitabine alone arm; two-sided p-value: 0.177). The calculated number of deaths for survival analysis with an 80% power to detect a 30% increase in median survival time in patients received lapatinib plus capecitabine was 457.
- 6) Due to the small number of deaths from causes other than breast cancer, the results of TTP analyses are similar to those of PFS analyses.
- 7) Study protocol was amended in December of 2004 to include trastuzumab as a required prior therapy. The impact of this amendment on efficacy results on all enrolled patients is small because only 6 patients enrolled without prior trastuzumab therapy, and the percentage of patients without trastuzumab as a prior therapy is similar between the arms (2 and 4 for combination arm and capecitabine alone arm respectively).
- 8) Study results based on all enrolled patients suggest that the combination arm was superior to the capecitabine alone arm with respect to time to disease progression or death due to breast cancer. Subgroup analyses by age and race also support this finding

## 5.2 Conclusions and Recommendations

In this reviewer's opinion, the study results from the submitted Phase III randomized multi-center, open-label trial support sponsor's claim of efficacy and 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 trastuzumab. 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 a hazard ratio of 0.55 per independently reviewed assessments, and 23.9 weeks versus 17.9 weeks with a 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 03 April 2006 analysis cut-off are not mature with 119 deaths.

## **SIGNATURES/DISTRIBUTION LIST**

Primary Statistical Reviewer: Chia-Wen Ko, Ph.D.  
Date: March 1, 2007

Concurring Reviewers: Rajeshwari Sridhara, Ph.D.  
Team Leader

Aloka Chakravarty, Ph.D.  
Director, Division of Biometrics V

cc:

HFD-150/Ms. Kim Robertson  
HFD-150/Dr. Qin Ryan  
HFD-150/Dr. Amna Ibrahim  
HFD-711/Dr. Chia-Wen Ko  
HFD-711/Dr. Rajeshwari Sridhara  
HFD-711/Dr. Aloka Chakravarty  
HFD-700/Dr. Robert O'Neill  
HFD-700/Ms. Lillian Patrician

c:\NDA\N022059\Statreview\_NDA22059.doc

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

Chia-wen Ko  
3/1/2007 03:08:37 PM  
BIOMETRICS

Rajeshwari Sridhara  
3/2/2007 09:44:49 AM  
BIOMETRICS

Concur with reviewer that lapatinib is effective. However, magnitude  
of effect can not be accurately evaluated due  
to missing data and consequences of interim analysis.

Aloka Chakravarty  
3/2/2007 02:10:40 PM  
BIOMETRICS