

MedDRA Preferred Terms	Lapatinib + capecitabine N = 198				Capecitabine N = 191			
	All	%	G3-4	%	All	%	G3-4	%
Ventricular dysfunction	1	1	0	0	2	1	0	0
Virilism	1	1	0	0	0	0	0	0
Abnormal sensation in eye	1	1	0	0	0	0	0	0
Diplopia	1	1	1	1	2	1	0	0
Eyelid edema	1	1	0	0	0	0	0	0
Eyelid pain	1	1	0	0	0	0	0	0
Keratitis	1	1	0	0	0	0	0	0
Photophobia	1	1	0	0	0	0	0	0
Visual acuity reduced	1	1	0	0	1	1	0	0
Xerophthalmia	1	1	0	0	0	0	0	0
Abdominal discomfort	1	1	0	0	1	1	0	0
Anal fissure	1	1	0	0	0	0	0	0
Aphthous stomatitis	1	1	0	0	1	1	0	0
Colitis	1	1	0	0	0	0	0	0
Epigastric discomfort	1	1	0	0	0	0	0	0
Faecal incontinence	1	1	0	0	0	0	0	0
Gastrointestinal haemorrhage	1	1	0	0	0	0	0	0
Gastrointestinal pain	1	1	0	0	0	0	0	0
Gingival bleeding	1	1	0	0	0	0	0	0
Gingivitis	1	1	0	0	2	1	0	0
Hiatus hernia	1	1	0	0	0	0	0	0
Mouth cyst	1	1	0	0	0	0	0	0
Oral mucosal exfoliation	1	1	0	0	0	0	0	0
Proctalgia	1	1	0	0	0	0	0	0
Rectal hemorrhage	1	1	0	0	0	0	0	0
Retching	1	1	0	0	0	0	0	0
Abasia	1	1	0	0	1	1	1	1
Axillary pain	1	1	0	0	2	1	0	0
Disease progression	1	1	1	1	1	1	1	1
Gait disturbance	1	1	0	0	2	1	1	1
Inflammation	1	1	0	0	1	1	0	0
Local swelling	1	1	0	0	0	0	0	0
Mucosal dryness	1	1	0	0	0	0	0	0
Necrosis	1	1	0	0	0	0	0	0
Budd-Chiari syndrome	1	1	0	0	0	0	0	0
Cholecystitis	1	1	0	0	0	0	0	0
Hepatic pain	1	1	0	0	1	1	0	0
Hepatotoxicity	1	1	0	0	1	1	0	0
Jaundice	1	1	0	0	0	0	0	0
Hypersensitivity	1	1	0	0	0	0	0	0
Cellulitis	1	1	1	1	2	1	0	0
Cystitis	1	1	0	0	2	1	0	0
Ear infection	1	1	0	0	1	1	0	0
Escherichia sepsis	1	1	1	1	0	0	0	0
Eye infection	1	1	0	0	2	1	0	0
Fungal infection	1	1	0	0	0	0	0	0
Fungal rash	1	1	0	0	0	0	0	0
Fungal skin infection	1	1	0	0	0	0	0	0
Gastroenteritis	1	1	0	0	1	1	0	0

MedDRA Preferred Terms	Lapatinib + capecitabine N = 198				Capecitabine N = 191			
	All	%	G3-4	%	All	%	G3-4	%
Genital infection fungal	1	1	0	0	0	0	0	0
Gingival abscess	1	1	0	0	0	0	0	0
Herpes zoster	1	1	0	0	0	0	0	0
Hordeolum	1	1	0	0	0	0	0	0
Pyelonephritis	1	1	0	0	0	0	0	0
Respiratory tract infection	1	1	0	0	1	1	0	0
Sialoadenitis	1	1	0	0	0	0	0	0
Tinea pedis	1	1	0	0	1	1	0	0
Back injury	1	1	1	1	0	0	0	0
Contusion	1	1	0	0	2	1	0	0
Fall	1	1	0	0	0	0	0	0
Medical device complication	1	1	0	0	0	0	0	0
Muscle strain	1	1	0	0	0	0	0	0
Thermal burn	1	1	0	0	1	1	0	0
Wound	1	1	0	0	1	1	0	0
Blood bicarbonate decreased	1	1	0	0	0	0	0	0
Blood chloride decreased	1	1	0	0	2	1	0	0
Blood creatine increased	1	1	0	0	0	0	0	0
Blood creatinine increased	1	1	0	0	1	1	0	0
Blood phosphorus decreased	1	1	0	0	0	0	0	0
Blood urea increased	1	1	0	0	1	1	0	0
Cardiac murmur	1	1	0	0	0	0	0	0
International normalised ratio increased	1	1	1	1	0	0	0	0
Neutrophil count	1	1	0	0	1	1	1	1
Neutrophil count increased	1	1	0	0	1	1	1	1
Protein total decreased	1	1	0	0	0	0	0	0
Respiratory rate increased	1	1	0	0	0	0	0	0
Acidosis	1	1	1	1	0	0	0	0
Hypercholesterolaemia	1	1	0	0	0	0	0	0
Hyperuricaemia	1	1	0	0	0	0	0	0
Hypoalbuminaemia	1	1	0	0	2	1	0	0
Hypocalcaemia	1	1	0	0	1	1	0	0
Hypochloraemia	1	1	0	0	0	0	0	0
Hypoproteinaemia	1	1	0	0	0	0	0	0
Lactose intolerance	1	1	0	0	0	0	0	0
Arthritis	1	1	1	1	1	1	0	0
Groin pain	1	1	0	0	0	0	0	0
Joint lock	1	1	1	1	0	0	0	0
Joint stiffness	1	1	0	0	0	0	0	0
Musculoskeletal discomfort	1	1	0	0	0	0	0	0
Osteonecrosis	1	1	1	1	0	0	0	0
Pain in jaw	1	1	0	0	1	1	0	0
Sensation of heaviness	1	1	0	0	0	0	0	0
Acute myeloid leukaemia	1	1	1	1	0	0	0	0
Malignant melanoma	1	1	1	1	0	0	0	0
Metastatic pain	1	1	1	1	0	0	0	0
Neoplasm skin	1	1	0	0	0	0	0	0
Balance disorder	1	1	0	0	2	1	0	0
Convulsion	1	1	1	1	1	1	0	0

MedDRA Preferred Terms	Lapatinib + capecitabine N = 198				Capecitabine N = 191			
	All	%	G3-4	%	All	%	G3-4	%
Coordination abnormal	1	1	0	0	1	1	1	1
Dizziness postural	1	1	0	0	0	0	0	0
Dysaesthesia	1	1	0	0	1	1	0	0
3rd nerve paralysis	1	1	0	0	0	0	0	0
Sensory disturbance	1	1	0	0	0	0	0	0
Somnolence	1	1	0	0	0	0	0	0
Spinal cord compression	1	1	1	1	0	0	0	0
Syncope vasovagal	1	1	1	1	0	0	0	0
Attention deficit/hyperactivity disorder	1	1	0	0	0	0	0	0
Confusional state	1	1	0	0	0	0	0	0
Emotional disorder	1	1	0	0	0	0	0	0
Mood altered	1	1	0	0	0	0	0	0
Tearfulness	1	1	0	0	0	0	0	0
Bladder pain	1	1	0	0	0	0	0	0
Hydronephrosis	1	1	0	0	0	0	0	0
Nephrolithiasis	1	1	0	0	0	0	0	0
Renal colic	1	1	0	0	0	0	0	0
Urinary incontinence	1	1	0	0	0	0	0	0
Genital pain female	1	1	0	0	0	0	0	0
Genital pruritus female	1	1	0	0	2	1	0	0
Genital tract inflammation	1	1	0	0	0	0	0	0
Vaginal discharge	1	1	0	0	3	2	0	0
Vaginal inflammation	1	1	0	0	0	0	0	0
Vulvovaginal discomfort	1	1	0	0	0	0	0	0
Asthma	1	1	1	1	0	0	0	0
Bronchospasm	1	1	1	1	0	0	0	0
Dry throat	1	1	0	0	0	0	0	0
Dyspnoea exacerbated	1	1	0	0	0	0	0	0
Haemoptysis	1	1	1	1	1	1	0	0
Hiccups	1	1	0	0	0	0	0	0
Hypoxia	1	1	1	1	0	0	0	0
Nasal congestion	1	1	0	0	4	2	0	0
Nasal discomfort	1	1	0	0	0	0	0	0
Nasal dryness	1	1	0	0	0	0	0	0
Pleural effusion	1	1	1	1	1	1	1	1
Rhinalgia	1	1	0	0	1	1	0	0
Sinus disorder	1	1	0	0	0	0	0	0
Erythema multiforme	1	1	0	0	0	0	0	0
Hair growth abnormal	1	1	0	0	0	0	0	0
Heat rash	1	1	0	0	0	0	0	0
Nail discolouration	1	1	0	0	0	0	0	0
Nail dystrophy	1	1	0	0	0	0	0	0
Nail toxicity	1	1	0	0	0	0	0	0
Pigmentation disorder	1	1	0	0	4	2	0	0
Rash generalised	1	1	0	0	3	2	0	0
Rash maculo-papular	1	1	0	0	0	0	0	0
Rash pruritic	1	1	0	0	2	1	0	0
Scab	1	1	0	0	0	0	0	0
Skin disorder	1	1	0	0	0	0	0	0

Clinical Review
 Qin Ryan, MD, PhD
 NDA 22059-000
 Tykerb (lapatinib)

MedDRA Preferred Terms	Lapatinib + capecitabine N = 198				Capecitabine N = 191			
	All	%	G3-4	%	All	%	G3-4	%
Skin exfoliation	1	1	0	0	2	1	0	0
Skin hypertrophy	1	1	0	0	0	0	0	0
Skin irritation	1	1	0	0	0	0	0	0
Hypotension	1	1	0	0	2	1	0	0
Vasodilatation	1	1	0	0	0	0	0	0

Source: Study EGF100151 study report.

7.1.7 Laboratory Findings

Clinical laboratory evaluation on hematology and chemistry parameters of study EGF 100151 were summarized as highest grade AE observed per each test and each subject. Laboratory AEs that occurred more than 2% in the combination arm, regardless relationship, were included in the table below.

Table 58: Study EGF 100151 Chemistry laboratory AEs ($\geq 2\%$) regardless of relationship (SP, Nov 15 2005 cut-off)

Laboratory Toxicities	Lapatinib + capecitabine AEs N = 164				Capecitabine AEs N = 152			
	All	%	G3-4	%	All	%	G3-4	%
Transaminase	98	60	8	5	90	59	6	4
Alk Phos	76	46	6	4	74	49	8	5
Bilirubin	73	45	6	4	40	26	3	2
Random Glucose	68	41	1	1	73	48	5	3
Potassium	49	30	4	2	40	26	5	3
Calcium	43	26	3	2	33	22	1	1
Albumin	35	21	3	2	35	23	1	1
Sodium	28	17	5	3	32	21	2	1
Urea	19	12	4	2	17	11	1	1
Bicarbonate	18	11	1	1	20	13	0	0
Creatinine	16	10	0	0	20	13	0	0
Hyperglycemia	3	2	3	2	1	1	1	1

Data source: Study EGF 100151 report

Table 59: Study EGF 100151 Chemistry laboratory AEs ($\geq 2\%$) regardless of relationship (SP, Apr 3 2006 cut-off)

Laboratory Toxicities	Lapatinib + capecitabine N = 198				Capecitabine N = 191			
	All	%	G3-4	%	All	%	G3-4	%
Transaminase	121	61	11	6	121	63	6	3
Alk Phos	100	51	7	4	100	52	8	4
Random Glucose	88	44	2	1	88	46	5	3
Bilirubin	86	43	7	4	86	45	5	3
Potassium	63	32	5	3	63	33	6	3
Calcium	52	26	3	2	52	27	1	1
Albumin	46	23	2	1	46	24	0	0
Sodium	32	16	5	3	32	17	2	1

Laboratory Toxicities	Lapatinib + capecitabine N = 198				Capecitabine N = 191			
	All	%	G3-4	%	All	%	G3-4	%
Creatinine	20	10	0	0	20	10	1	1
Urea	19	10	0	0	19	10	2	1
Bicarbonate	18	9	1	1	18	9	0	0
BUN	3	2	1	1	3	2	0	0
Hypokalemia	2	1	2	1	2	1	0	0
Hypercalcemia	1	1	1	1	1	1	2	1
Hypocalcemia	1	1	1	1	1	1	1	1

Data source: Study EGF 100151 report

Reviewer: The most common laboratory AEs were abnormalities of transaminase, alkaline phosphatase, potassium, calcium and albumin. With the caveat that the capecitabine dose is 25% higher for the control arm, laboratory AEs were similar between the two arms. The incidence of grade 3-4 laboratory AEs were similar between the two arms, 28% in combination arm and 22% in capecitabine arm at the time of interim analysis, and 29% in combination arm and 22% in capecitabine arm at the time of clinical up date.

Table 60: Study EGF 100151 hematology laboratory AEs ($\geq 2\%$) regardless of relationship (SP, Nov 15 2005 cut-off)

Laboratory Toxicities	Lapatinib + capecitabine AEs N = 164				Capecitabine AEs N = 152			
	All	%	G3-4	%	All	%	G3-4	%
Hemoglobin	96	59	1	1	86	57	1	1
Lymphocytes	75	46	16	10	83	55	15	10
WBC	65	40	0	0	72	47	5	3
Neutrophils	39	24	4	2	44	29	6	4
Platelets	29	18	0	0	23	15	1	1
Lymphopenia	6	4	6	4	2	1	2	1
Granulocytes	3	2	0	0	5	3	1	1

Data source: Study EGF 100151 report

Table 61: Study EGF 100151 hematology laboratory AEs ($\geq 2\%$) regardless of relationship (SP, Apr 3 2006 cut-off)

Laboratory Toxicities	Lapatinib + capecitabine N = 198				Capecitabine N = 191			
	All	%	G3-4	%	All	%	G3-4	%
Hemoglobin	118	60	1	1	118	62	6	3
Lymphocytes	98	49	17	9	98	51	17	9
WBC	82	41	1	1	82	43	4	2
Neutrophils	48	24	9	5	48	25	9	5
Platelets	37	19	1	1	37	19	1	1
Granulocytes	3	2	0	0	3	2	1	1
Granulocytopenia	1	1	1	1	1	1	1	1
Leukopenia	1	1	1	1	1	1	1	1
Lymphopenia	1	1	1	1	1	1	2	1

Data source: Study EGF 100151 report

Reviewer: The most common hematological laboratory AEs were neutropenia and thrombocytopenia. Due to the lower dose (20%) of capecitabine for combination arm, less neutropenia was observed in the combination arm at both interim analysis and clinical up date, 24% vs 29% and 24% vs. 25%, respectively. Other laboratory AEs were similar between the two arms. The incidence of grade 3-4 laboratory AEs were similar between the two arms, 17% in combination arm and 21% in capecitabine arm at the time of interim analysis, and 20% in combination arm and 24% in capecitabine arm at the time of clinical up date.

7.1.8 Vital Signs

Study subject's vital signs (blood pressure, heart rate, body weight and temperature) were measured at each clinic visit. The reviewer's verified and confirmed applicant's analysis that there were no clinically significant trends in the vital signs of either treatment group.

7.1.9 Electrocardiograms (ECGs) in Study 100151 and QT study.

At the time of clinical up date, there were 95% of combination arm and 96% of control arm subjects had a base line ECG. For subjects who withdraw from treatment, 38% of the combination arm and 21% of control arm subjects had a withdraw ECG. The limited ECG findings were similar at screening and withdrawal between the treatment groups, as shown in the table.

Table 62: Study EGF 100151 Electrocardiogram Findings (SP, Nov 15 2005 cut-off)

ECG Finding/ Arm	Lapatinib+ Capecitabine		Capecitabine	
	Nov 15 2005 N=164 n (%)	Apr 3 2006 N=198 (%)	Nov 15 2005 N=152 n (%)	Apr 3 2006 N=191 (%)
Screening n	N = 154 (94)	N = 190 (96)	N = 144 (95)	N =183 (96)
Normal	128 (83)	155 (82)	120 (83)	152 (83)
Abnormal, not clinically significant	24 (16)	33 (17)	22 (15)	28 (15)
Abnormal, clinically significant	2 (1)	2 (10)	1 (<1)	2 (1)
Missing	0	0	1 (<1)	1(<1)
Withdrawal n	N = 53 (32)	N = 76 (38)	N = 44 (29)	N = 59 (31)
Normal	41 (77)	59 (78)	35 (80)	48 (81)
Abnormal, not clinically significant	11 (21)	15 (20)	9 (20)	11 (19)
Abnormal, clinically significant	1 (2)	2 (3)	0	0

Data source: Study EGF 100151 report

Reviewer: Based on the limited data, all ECGs at withdrawal were either normal or abnormal but not clinically significant, except one subject in the lapatinib + capecitabine arm were identified to have an abnormal ECG with clinical significance at withdrawal. No detail on two isolated ECG abnormalities were provided in the NDA submission. This event was not identified as an AE by MedDRA criteria.

The FDA clinical pharmacology reviewers reviewed clinical pharmacology data (please see clinical pharmacology review for details) and come to the following conclusion. The QT prolongation

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

7.1.10 Immunogenicity

Not applicable

7.1.11 Human Carcinogenicity

No data available.

7.1.12 Special Safety Studies

See pharmacology review on QTc analysis.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

None.

7.1.14 Human Reproduction and Pregnancy Data

Table 63: Study EGF 100151 study subjects' reproductive potential at baseline (ITT)

	Lapatinib+ Capecitabine N=163	Capecitabine N=161	All Subjects N=324
Child-bearing Potential, n (%)			
Postmenopausal	129 (79)	115 (71)	244 (75)
Potentially able to conceive	19 (12)	29 (18)	48 (15)
Sterile	14 (9)	16 (10)	30 (9)
Premenarchal	1 (<1)	1 (<1)	2 (<1)

Data Source: Study EGF 100151 report.

No pregnancy reported in study EGF100151. Although lapatinib did not impair fertility when administered to either male or female rats prior to and during the mating period, the effect of lapatinib on human fertility is unknown. However, lapatinib did lead to a dramatic increase in neonatal loss (91%) in rats during the first week of life. Therefore, lapatinib may cause fetal harm when administered to a pregnant woman.

7.1.15 Assessment of Effect on Growth

Not applicable.

7.1.16 Overdose Experience

Two cases of over dose were reported with 1250 mg BID for 5-7 days. Both subjects had severe nausea, vomiting and diarrhea, require hospitalization. Both subjects were recovered without consequence.

7.1.17 Post marketing Experience

None.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The exposure analysis is primarily based on study 100151 data set, which is the only data set that provided lapatinib and capecitabine combination in compare to capecitabine alone.

7.2.2 Dose Intensity and Duration

The exposure of study medication for each arm were summarized by the applicant and verified by the reviewer (table below).

Table 64: Study EGF 100151 treatment exposure (SP, Nov 15, 2005 cut-off)

	Lapatinib + Capecitabine N=164		Capecitabine N=152
Medication	Lapatinib	Capecitabine	Capecitabine
Subjects Exposed to Each Drug, N	164	163	152
Duration of Treatment, weeks			
Mean (SD)	19.3 (16.09)	18.9 (15.93)	13.6 (11.84)
Median	16.1	15.7	9.4
Range	0-80	0-80	0-55
Daily Dose, mg or mg/m²			
Mean (SD)	1247.6 (150.45)	1904.4 (359.14)	2315.6 (434.12)
Median	1250.0	2000.0	2376.8
Range	788-3036	865-4000	1192-4300
Cumulative Dose, mg or mg/m²			
Mean (SD)	161747.6 (137502.18)	159362.0 (123696.79)	143977.5 (113111.63)
Median	131875.0	120500.0	105000.0
Range	2500-701250	3300-610000	1500-516250

Data source: Study EGF 100151 report

Reviewer: The mean duration of exposure to study medication was slightly longer in the lapatinib + capecitabine arm (19.3 and 18.9 weeks) than in the capecitabine arm (13.6 weeks). This difference may be due to the shorter time to disease progression in the capecitabine group compared to the lapatinib + capecitabine resulting in treatment termination.

The dose intensity and duration at the time of clinical update (Apr 3 2006) are summarized as follow.

Table 65: Study EGF 100151 treatment exposure (SP, Apr 3 2006 cut-off)

	Lapatinib + Capecitabine N=198		Capecitabine N=191
Medication	Lapatinib	Capecitabine	Capecitabine
Subjects exposed to each drug, n (%)	198	196	191
Duration of Treatment, weeks			
Mean (StdD)	21.6 (18.14)	20.7 (17.35)	15.1 (13.80)
Median	19.0	17.5	9.7
Range	0 – 100	0 – 90	0 – 67
Daily Dose, mg or mg/m²			
Mean (StdD)	1252.0 (164.77)	1864.0 (292.25)	2273.6 (302.24)
Median	1250.0	2000.0	2413.8
Range	777 – 3036	813 – 2947	1192 – 2549
Cumulative Dose, g or g/m²			
Mean (StdD)	182.67 (155.933)	170.00 (128.569)	153.53 (126.287)
Median	160.625	145.900	105.000
Range	3.75 – 875.0	5.4 – 728.0	4.84 – 560.0

Data source: Study EGF 100151 report

Reviewer: With a later cut-off date (Apr 3 2006), the treatment duration and cumulative dose were increased but continue the trend noted in the interim analysis. The mean duration of exposure to study medication was longer in the lapatinib + capecitabine group (21.6 and 20.7 weeks) than in the capecitabine group (15.1 weeks). This is likely due to the shorter time to disease progression in the capecitabine group compared to the lapatinib + capecitabine resulting in treatment termination.

7.2.3 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.3.1 Other studies

None.

7.2.3.2 Post marketing experience

None.

7.2.3.3 Literature

None.

7.2.4 Adequacy of Overall Clinical Experience

Adequate number of subjects were exposed to the lapatinib alone and in combination with capecitabine. The doses and durations of exposure in study EGF 100151 were adequate to assess safety for the intended use in refractory, Her 2 positive, metastatic breast cancer patients. The design of study 100151 (open label and active-control) was adequate to address the adverse event for lapatinib and capecitabine combination versus capecitabine alone. The study also evaluated potential cardiac effects of lapatinib and whether were suggested by herceptin experience but was not suggested by lapatinib preclinical data assessed. However, the patients excluded from the study, such as uncontrolled diabetics, people with recent myocardial infarction, people with renal or hepatic functional impairment, or people on medications that are known CYP3A4 and CYP 3A5 inhibitors or inducers limited the relevance of safety assessments.

7.2.5 Adequacy of Special Animal and/or In Vitro Testing

See Toxicology review.

7.2.6 Adequacy of Routine Clinical Testing

The effort of routine clinical testing of study subjects, including efforts to monitor laboratory parameters, vital signs, ECGs, and efforts to elicit adverse event data were adequate, including adequacy of the methods and tests used and the frequency of testing.

7.2.7 Adequacy of Metabolic, Clearance, and Interaction Workup

The details of these assessments is in section 5 and the Clinical Pharmacology Review, in which case this section can refer to them.

7.2.8 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The adequacy of the applicant's efforts to detect specific adverse events that are potentially problematic and might be expected with lapatinib, such as cardiac toxicity, was adequate. However, the applicant should continue to monitor the potential cardiac toxicity under long term use and post marketing.

7.2.9 Assessment of Quality and Completeness of Data

The reviewer's overall assessment on the quality and completeness of the primary data of study EGF 100151 and supportive data of studies EGF 20002 and EGF 20008 available for conducting the safety review is that the data are adequate.

7.2.10 Additional Submissions, Including Safety Update

The data of safety up date of study EGF 100151 supporting the initial safety data, as detailed in various adverse event sections.

7.3 Summary of Selected Adverse Events, Important Limitations of Data, and Conclusions

The safety analyses indicated that oral lapatinib 1250 mg once daily taken continuously in combination with 2000 mg/m²/day capecitabine for 14/21 days has an acceptable risk-benefit ratio in patients with advanced/metastatic breast cancer. It is note worthy that the capecitabine dose was 25% higher (2500 mg/m²) for the control arm, capecitabine alone.

1. With the 25% higher capecitabine dose in the control arm, the incidence of AEs was similar between the treatment groups (89% for lapatinib + capecitabine and 91 for capecitabine). Diarrhea, PPE, nausea, rash, vomiting and fatigue were the most common AEs reported for the combination arm. Diarrhea and rash were more common in the lapatinib + capecitabine arm (60% and 27%, respectively) than in the capecitabine arm (39% and 15%). Incidence of PPE, nausea and vomiting was similar between the two treatment arms. On the other hand, fatigue was more common in the capecitabine group (27%) than in the lapatinib + capecitabine arm (18%), as were anorexia (20% vs. 15%), abdominal pain (16% vs. 10%), and asthenia (12% versus 6%). No interstitial pneumonia or pneumonitis observed during this study.
2. The incidence of SAEs was similar between the treatment groups (24% in each). The most common SAE was diarrhea and PPE for both arms, 13% and 7% for lapatinib/capecitabine arm versus 11% and 11% for capecitabine arm.
3. There was no death on lapatinib combination arm during the first 60 days of study. The 100 day death was 4% at the interim analysis (Nov 15 2005 cut-off) and 5% at the clinical up date (Apr 3 2006 cut-off), all due to disease progression. The fatal AEs reported on lapatinib combination arm were less than 2% and occurred after 100 days on study. There was no identifiable pattern to raise any clinical concern.

4. The proportion of subjects who discontinued study due to an AE was similar in both the lapatinib + capecitabine (13%) and capecitabine groups (12%). Diarrhea was the most common AE resulting in treatment termination, 5% for lapatinib/capecitabine arm and 3% for capecitabine arm.

5. Overall analysis on relative change of LVEF from baseline indicated there is no decline in mean LVEF in either arm from baseline through 6 months. At the time of clinical update, there were 7 patients (4%) in lapatinib + capecitabine combination arm and 1 patient in capecitabine arm experienced a decreased LVEF during the study. All seven events in the lapatinib + capecitabine group were considered drug related by the investigator. Five of the seven events in the lapatinib + capecitabine group were asymptomatic (grade 2 or less), one were symptomatic and one without classification. Four of them were classified as SAEs (\geq grade 2). None of these was fatal or lead to treatment termination. At the time of interim analysis, two of the LVEF AEs were thought to be not reversible; but by the time of clinical update, only one LVEF AE was not reversible. However, a follow up 8 months after the safety update cut-off indicated that this case was resolved without sequelae.

6. Approximately 75% cases of diarrhea events were grade 1 or 2. More subjects in the lapatinib-capecitabine combination arm (98 of 164 subjects; 60%) had diarrhea than in the capecitabine arm (60 of 152 subjects; 39%). More subjects in the capecitabine group (20%) than in the lapatinib + capecitabine group (11%) had a diarrhea (including diarrhea, hemorrhagic diarrhea and infectious diarrhea) SAE and one subject in the capecitabine group had a fatal diarrhea SAE with vomiting and small bowel obstruction (see fatal AEs). Eight (5%) subjects in the combination group and 4 (3%) subject in the monotherapy group withdrew from the study due to diarrhea. The difference in the incidence of diarrhea AEs was due to an increased number of grade 1 or 2 toxicity reports in the lapatinib + capecitabine group. The less number of severe diarrheas in the lapatinib combination arm may be due to the lower dose of capecitabine administered.

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

8. More subjects in the lapatinib + capecitabine arm (27%) had rash than in the capecitabine arm (15%). This difference was mainly due to increased incidences of grade 1 in the combination arm and few of rash events led to termination of study treatment (3 subjects on the combination arm and none in capecitabine arm).

9. No subjects in either treatment group experienced an interstitial pneumonia/pneumonitis event during the study.

10. Hematology and clinical chemistry toxicities were reflective of patients with metastatic breast cancer and treatment with capecitabine and were reported with a similar incidence in both treatment

groups, with the caveat that the capecitabine dose was 25% higher for the control arm. The most common laboratory AEs were abnormalities of potassium, calcium and albumin, neutropenia and thrombocytopenia. Due to the lower dose of capecitabine for combination arm, less neutropenia was observed in the combination arm, 24% vs. 28%. Other laboratory AEs were similar between the two arms. The incidence of grade 3-4 laboratory AEs were also similar between the 2 arms, 20% in combination arm and 21% in capecitabine arm.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Base on the safety review, the reviewer would recommend the proposed dose/regimen for lapatinib use. The proposed dose of TYKERB is 1,250 mg (5 tablets) once daily (continuously) in combination with capecitabine 2,000 mg/m²/day (administered orally in 2 doses approximately 12 hours apart) on days 1-14 in a 21 day cycle. The safety analysis from study EGF 100151 indicated that the safety profile of lapatinib in combination with capecitabine is acceptable with the efficacy of the regimen in mind.

Special management and dose modification:

QTC prolongation: Based on the review of clinical pharmacology data by the FDA clinical pharmacology reviewers, QT prolongation was observed in an uncontrolled, open-label dose escalation study of lapatinib in advanced cancer patients. Lapatinib should be administered with caution to patients who have or may develop prolongation of QTc. These conditions include patients with hypokalemia or hypomagnesemia, with congenital long QT syndrome, patients taking anti-arrhythmic medicines or other medicinal products that lead to QT prolongation, and cumulative high-dose anthracycline therapy. Hypokalemia or hypomagnesemia should be corrected prior to lapatinib administration. The prescriber should consider an on-treatment electrocardiogram with QT measurement.

Cardiac Events: Lapatinib should be discontinued in patients with a decreased left ventricular ejection fraction (LVEF) that is grade 2 or greater by NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) and in patients with an LVEF that drops below the institution's lower limit of normal (see Warnings and Precautions [5.1] and Adverse Reactions [6.1]). Lapatinib may be restarted at a reduced dose (1,000 mg/day) after a minimum of 2 weeks and if the LVEF recovers to normal and patient is asymptomatic.

Hepatic Impairment: Patients with severe hepatic impairment (a Child-Pugh score >9) should have their lapatinib dose reduced. A dose reduction to 750 mg/day in patients with severe hepatic

impairment is predicted to adjust the AUC to the normal range and should be considered. However, there is no clinical data in this setting.

Concomitant Strong CYP3A4 Inhibitors: The use of concomitant strong CYP3A4 inhibitors should be avoided (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole). Grapefruit may also increase plasma concentrations of lapatinib and should be avoided. If patients must be co-administered a strong CYP3A4 inhibitor, based on pharmacokinetic studies, a dose reduction to 500 mg/day of lapatinib is predicted to adjust the lapatinib AUC to the range observed without inhibitors and should be considered. However there is no clinical data in this setting. If the strong inhibitor is discontinued, a washout period should be allowed before the lapatinib dose is adjusted upward to the indicated dose. (see section 8.2).

Concomitant Strong CYP3A4 Inducers: The use of concomitant strong CYP3A4 inducers should be avoided (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, St. John's Wort). If patients must be co-administered a strong CYP3A4 inducer, based on pharmacokinetic studies, a dose titration from 1250 mg/day up to 4500 mg/day of lapatinib is predicted to adjust the lapatinib AUC to the range observed without inducers and should be considered. Because there is no clinical data in this setting, the dose should be gradually titrated upwards. If the strong inducer is discontinued the lapatinib dose should be adjusted downward to the indicated dose. (see section 8.2)

Other Toxicities: Discontinuation or interruption of dosing with lapatinib may be considered when patients develop greater than or equal to grade 2 NCI CTC toxicity and can be restarted at 1,250 mg/day when the toxicity improves to grade 1 or less. If the toxicity recurs, then LAPATINIB should be restarted at a lower dose (1,000 mg/day).

8.2 Drug-Drug Interactions

8.2.1 Drugs that Inhibit or Induce Cytochrome P450 3A4 Enzymes

Lapatinib undergoes extensive metabolism by CYP3A4, and concomitant administration of strong inhibitors or inducers of CYP3A4 alter lapatinib concentrations significantly (see sections Ketoconazole and Carbamazepine, below). Dose adjustment of lapatinib should be considered for patients who must receive concomitant strong inhibitors or concomitant strong inducers of CYP3A4 enzymes (see section 8.1).

Ketoconazole: In healthy subjects receiving ketoconazole, a CYP3A4 inhibitor, at 200 mg twice daily for 7 days, systemic exposure (AUC) to lapatinib was increased to approximately 3.6-fold of control and half-life increased to 1.7-fold of control.

Carbamazepine: In healthy subjects receiving the CYP3A4 inducer, carbamazepine, at 100 mg twice daily for 3 days and 200 mg twice daily for 17 days, systemic exposure (AUC) to lapatinib was decreased approximately 72%.

8.2.2 Drugs that Inhibit Drug Transport Systems

Lapatinib is a substrate of the efflux transporter P-glycoprotein (Pgp, ABCB1). If lapatinib is administered with drugs that inhibit Pgp, increased concentrations of lapatinib are likely, and caution should be exercised.

8.2.3 Other Chemotherapy Agents

In separate studies, concomitant administration of lapatinib with capecitabine or trastuzumab did not meaningfully alter the pharmacokinetics of these agents (or the metabolites of capecitabine) or lapatinib.

8.3 Special Populations

As the majority of subjects in the safety population, 87% subjects (274/316) were less than 65 years of age no meaningful comparison could be made by age (<65 years and \geq 65 years).

As 90% of patients in study EGF 100151 were white, no meaningful comparisons between the racial groups could be made by race (white, black, Asian, American Indian, Hispanic and other).

8.4 Pediatrics

Not applicable.

8.5 Advisory Committee Meeting

None.

8.6 Literature Review

More than 400,000 deaths annually worldwide caused by breast cancer, making metastatic breast cancer the leading cause of cancer deaths in women¹. Patients whose tumors have progressed on hormone therapy are candidates for cytotoxic chemotherapy. Patients with hormone receptor-negative tumors and those with visceral metastases are also candidates for cytotoxic agents. Many single agent or combination chemotherapy regimen has shown antitumor activity in metastatic breast cancer as outlined below.

Table 66: Chemotherapy options for metastatic breast cancer patients

Class / Name	Agents
Single agents	
Anthracyclines.	Doxorubicin. Epirubicin. Liposomal doxorubicin. ²⁻⁴ Mitoxantrone
Taxanes.	Paclitaxel. Docetaxel. Albumin-bound nanoparticle paclitaxel (ABI-007 or Abraxane). ^{5,6}
Alkylating agents.	Cyclophosphamide.
Fluoropyrimidines.	Capecitabine. ^{7,8} 5-FU.
Antimetabolites.	Methotrexate.
Vinca alkaloids	Vinorelbine. ⁹ Vinblastine. Vincristine
Platinum	Carboplatin. Cisplatin
Other	Gemcitabine. ¹⁰ Mitomycin C
Combination regimens	
CA	cyclophosphamide and doxorubicin. ¹¹
AT	Docetaxel and doxorubicin. ¹² or Doxorubicin and paclitaxel. ^{13,14}
CAF	cyclophosphamide, doxorubicin, 5-fluorouracil. ¹⁵
CMF	cyclophosphamide, methotrexate, 5-fluorouracil. ¹⁶
TC	Docetaxel and capecitabine. ¹⁷
VE	Vinorelbine and epirubicin. ¹⁸

Approximately 25% of patients with breast cancers that overexpress the epidermal growth factor receptor type 2 (ErbB2 or HER2/neu,) are at greater risk for disease progression and death than those whose tumors do not overexpress ErbB2¹⁹. Therapeutic strategies have been developed to block ErbB2 signaling pathways to improve the efficacy of chemotherapy regimens in women with ErbB2 positive breast cancer. Trastuzumab, a recombinant humanized monoclonal antibody against the extracellular domain of the ErbB2 protein, is used to treat both metastatic and early-stage ErbB2-positive breast cancers^{20,21}.

In patients previously treated with cytotoxic chemotherapy whose tumors overexpress HER2/neu, administration of Herceptin as a single agent resulted in a response rate of 21%. In a prospective trial, patients with metastatic disease were randomized to receive either chemotherapy alone (doxorubicin and cyclophosphamide or paclitaxel) or the same chemotherapy and Herceptin. Patients treated with chemotherapy plus Herceptin had an overall survival (OS) advantage as compared with those receiving chemotherapy alone (25.1 months vs. 20.3 months, P = .05).²⁰ When combined with doxorubicin, Herceptin is associated with significant cardiac toxicity.²²

Consequently, patients with metastatic breast cancer with substantial overexpression of HER2/neu are candidates for treatment with the combination of Herceptin and paclitaxel or for clinical studies of Herceptin combined with taxanes and other chemotherapeutic agents.²³

Trastuzumab is currently the only treatment registered for use in first line ErbB2 positive metastatic breast cancer in combination with paclitaxel²⁰ and recently has demonstrated clinical benefit in the ErbB2 positive adjuvant breast cancer setting.^{24, 25} After taxane (paclitaxel or docetaxel), vinorelbine and gemcitabine-based trastuzumab combination therapy, resistance of ErbB2 positive breast cancer to trastuzumab eventually occurs in the metastatic setting and some patients develop recurrence following adjuvant therapy with trastuzumab. There remains a need for alternative therapies to block ErbB2 signaling pathways when this occurs.^{26, 27} It is common clinical practice after progression on a trastuzumab regimen, to change the cytotoxic component of the regimen while maintaining the biologic component. 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 use in the treatment of patients with metastatic breast cancer resistant to anthracyclines and taxanes. It is an oral drug with an acceptable safety profile. Capecitabine or Gemcitabine has been used in combination of trastuzumab in Her2 over expressing breast cancer patients who progressed after anthracyclin, taxane and herceptin containing regimen. There is however no approved therapy for patients whose tumors have progressed on trastuzumab.

Alternative treatment strategies have become necessary, as the clinical outcome of subjects who receive trastuzumab-based therapy for metastatic disease may not be influenced by continuing trastuzumab therapy beyond progression of disease. Recent retrospective studies suggest that response rate, overall survival, and time to second progression are similar between patients that continue on trastuzumab-based therapy and those that discontinue trastuzumab.²⁷ Trastuzumab resistance may present a treatment dilemma in the future, not only for patients whose tumors progress in the metastatic setting but also for patients that receive trastuzumab in the adjuvant setting. In an ErbB2 positive metastatic breast cancer setting, for patients whose tumors have progressed after anthracycline, taxane and trastuzumab treatment, there is a clear medical need for new effective treatments

Lapatinib, an oral, small molecule, dual tyrosine kinase inhibitor of ErbB2 and ErbB1 (EGFR),^{28, 29} has demonstrated non-cross-resistance with trastuzumab in preclinical studies.³⁰ In vitro data suggest that capecitabine therapy in combination with ErbB inhibitors can have synergistic activity in both high and low ErbB expressing breast cancer cell lines.³¹ Activity in women with ErbB2 positive metastatic breast cancer progressing on trastuzumab has been demonstrated in single arm clinical studies, as reported in this NDA submission.³² To support the efficacy of this NDA, a randomized open label study, EGF 100151³³, tested lapatinib in combination with capecitabine in the setting of ErbB2 positive metastatic breast cancer that has been treated with anthracyclines, taxanes and trastuzumab as the sole information for this NDA review.

8.7 Post marketing Risk Management Plan

None

9 OVERALL ASSESSMENT

9.1 Conclusions

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

9.2 Recommendation on Regulatory Action

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

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

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

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

The toxicity of the lapatinib-containing arm was no worse than the capecitabine alone, except for increased incidence of diarrhea and rash. This may be because capecitabine doses were 25% higher in the control arm. There is a small incidence of decrease in left ventricular systolic function but this is generally reversible. QT prolongation has been observed with lapatinib use but Torsade de

Pointes has not been reported. The risk-benefit ratio favors the approval of this combination for the said indication.

9.3 Recommendation on Post marketing Actions

9.3.1 Risk Management Activity

None. Please see Office of Safety review for details.

9.3.2 Required Phase 4 Commitments

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

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

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

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

9.3.3 Other Phase 4 Requests

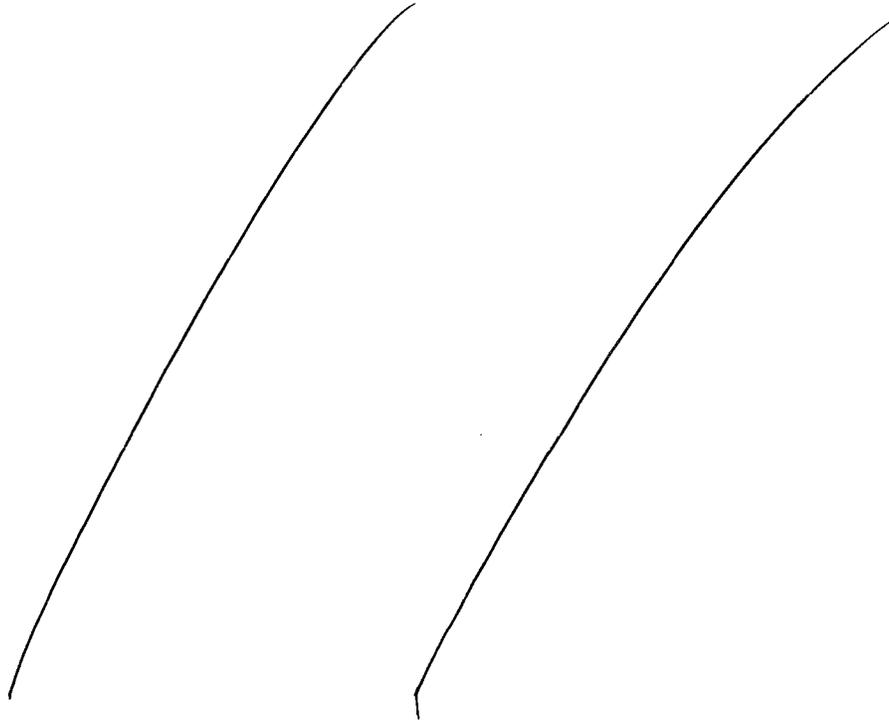
None

9.4 Labeling Review

As detailed in line-by line review, the medical team made following revision to the proposed label.



Clinical Review
Qin Ryan, MD, PhD
NDA 22059-000
Tykerb (lapatinib)



10 APPENDICES

10.1 Review of Individual Study Reports

Studies reviewed: Study EGF100151, Study EGF 20002, Study EGF 20008, and Study EGF 10005.

10.1.1 Study EGF100151

10.1.1.1 Protocol and Amendment Review

The italic sections in this review were taken as is from the protocol. The original protocol and all later amended versions are available in the EDR (submission date 9/15/2006). The protocol of study EGF 100151 has been submitted for special protocol assessment. The original protocol was dated 2003-Aug-7 and was used from the beginning of the study. Subsequently, 6 amendments were made to the protocol as outlined below:

Table 67: Timeline of study EGF 100151 amendments and mile stones

Date	Protocol Version and Milestone Description
2003-Aug-07	Original
2004-Jan-29	Amendment 1: Country specific mandated (Spain) for the sponsor to supply all medications required to be administered during all clinical trials.
2004-Mar-03	The first subject was randomized.
2004-May-04	Amendment 2: Provided further clarification to study design, conduct, and update relevant sections to reflect current clinical practice.
2004-Jul-23	Amendment 3: Amendment for the pharmacogenetic research to be conducted on blood samples collected from consenting subjects as part of study EGF100151. This amendment only applied in Italy to comply with the "Italian Proposed Guideline for the Evaluation of Pharmacogenetic Research."
2004-Sep-10	Amendment 4: Country specific Amendment for Germany only, mandated by German Central Ethics Committee to add the exclusion of birth control methods that include estrogen and limited use of methods that include progestogen.
2004-Dec-03*	Amendment 5: Global Amendment with key changes of eligibility requirement to require that all subjects have prior trastuzumab; power the trial for the secondary endpoint of overall survival; clarify some study procedures; clarify tumor genetics.
2005-Aug-02*	Amendment 6: Global Amendment with key change of updated prohibited medication section.
2005-Nov-15	The protocol pre-specified 1st interim analysis was conducted with this clinical cut off date
2006-Mar-20	Based on the first interim analysis, IDMC suggested that the results justified halting further enrollment into the study per protocol and that subjects in the capecitabine group be informed of results and given the opportunity to receive lapatinib + capecitabine.
2006-April-03	GSK terminated subject enrollment.
2006-May-12*	Amendment 7: Global Amendment with key changes to the study design because enrollment was halted due to positive results in interim analysis and updating the prohibited medication table.

Source: EGF100151 study report.

* Significant amendment, detailed review follows.

Reviewer: This protocol review focuses on the original protocol and amendments 2, 5 and 6.

The sponsor has informed FDA with IDMC's recommendation on Mar 23, 2006. FDA also contacted IDMC to verify the information and contacted EMEA to understand their position.

10.1.1.1.1 Title

A Phase III, Randomized, Open-Label, Multicenter Study Comparing GW572016 and Capecitabine (Xeloda) versus Capecitabine in Women with Refractory Advanced or Metastatic Breast Cancer

10.1.1.1.2 Study Center(s)

This study was carried out at 128 centers in the following countries: Argentina, Australia, Brazil, Canada, Finland, France, Germany, Greece, Hong Kong, Ireland, Israel, Italy, Poland, Portugal, Russia, Republic of South Africa, Spain, Switzerland, United Kingdom, and the United States.

10.1.1.1.3 Objectives

Primary Objective: To evaluate and compare time to progression (TTP) in subjects with refractory advanced or metastatic breast cancer treated with lapatinib and capecitabine versus capecitabine alone.

Secondary Objectives:

- *To evaluate and compare the two treatment arms with respect to:*
 - *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*
 - *6-month progression-free survival*
 - *Overall survival*
- *To compare the qualitative and quantitative toxicity associated with oral capecitabine administered with lapatinib to that of capecitabine alone;*
- *To evaluate and compare the two-treatment arms with respect to change in quality of life (QOL) status relative to baseline (this will be analyzed and reported separately)*
- *To compare tumor response rates following the lapatinib and capecitabine therapy to baseline and on-treatment serum concentrations of ErbB1 and ErbB2*

- *To further characterize the patient population by determination of intra-tumoral expression of ErbB1 (Epidermal Growth Factor Receptor -EGFR), ErbB2 and downstream biomarkers which may help elucidate the effects of lapatinib on the target and other proteins along relevant pathways in the tyrosine kinase pathway.*

Pharmacogenetic:

- To determine the intra-tumoral genetic changes (i.e., mutations, copy number variability, expression levels) that may correlate with response to lapatinib, by either direct (i.e., sequencing of ErbB1-4 or other cancer-related genes) or genome-wide methods (for example, array comparative genomic hybridization) (this were to be analyzed and reported separately)

10.1.1.1.4 Study Design:

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

Approximately 372 female subjects (186 in each arm) will be enrolled. Subjects were to be randomized to one of two treatment arms, to receive either GW572016 1250 mg/day and capecitabine 2000 mg/m²/day Days 1-14, every 21 days or capecitabine 2500 mg/m²/day Days 1-14, every 21 days alone. Randomization were to be stratified according to the following:

3. Stage of Disease
 - Stage IIIB
 - Stage IV
4. Site of disease were to be assigned to 1 of 2 categories:
 - Visceral
 - Non-visceral

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

Clinical and laboratory parameters were to be assessed to evaluate disease response and toxicity of randomized therapy. Safety and efficacy assessments were to be performed every 6 weeks for the first 24 weeks, then every 12 weeks and at the end of treatment. Additional safety assessments were to be performed on all subjects every 3 weeks and at the end of treatment. Subjects withdrawn from investigational drug who had not progressed were to be assessed every 12 weeks until progression. Thereafter, subjects were to be followed for survival at approximately 12-week intervals until death.

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

Reviewer: The applicant has notified FDA about IDMC's recommended actions and this amendment.

10.1.1.1.5 Treatment, Dose Modification and Treatment Termination

The recommended dose for the combination arm for this study is based on data from the EGF10005 Phase I study in which GW572016 is administered with capecitabine. The maximum tolerated dose was reached with the regimen of GW572016 1250 mg per day and capecitabine 2000 mg/m²/day administered in divided doses.

Table 68: Treatment plan

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

APPEARS THIS WAY
ON ORIGINAL

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Dose modification for capecitabine and lapatinib combination arte as follows:

Table 69: Toxicity and dose modification:

Toxicity NIC-CTCAE Grade	During Course of Therapy	GW572016	Capecitabine
Grade 1	Maintain dose	No change	No change
Grade 2 Specific Events Hematology –ANCs <1.0 × 10⁹/L Platelet count is <75.0 × 10⁹/L Hemoglobin is <9.0 g/dL (after transfusion if needed Chemistry-Bilirubin is ≥2 times ULN (unless Bilirubin was higher at study entry and has not yet fallen below 2X ULN) Serum Creatinine >1.5 mg/dL Calculated Creatinine Clearance ≤ 40ml/min	GW572016 - Interrupt treatment until resolved to grade 0-1, up to 14 days. Capecitabine- Interrupt treatment until resolved to grade 0-1, up to 14 days IF Toxicity does not resolve consult GSK Medical Monitor, to determine if it is in the best interest of the patient to continue in the study.	1st appearance-Resume 100%, 2nd appearance-Resume 100% or dose reduce to 1000 mg/day. 3rd appearance-Resume 100% or dose reduce to 1000 mg/day	1st appearance-Resume 100%, 2nd appearance-Resume 75% (rounded to nearest 150 mg), 3rd appearance discontinue permanently
Grade 2-Any other event Except toxicity of Cardiac Ejection Fraction*	GW572016 -Maintain dose. Capecitabine-Interrupt treatment until resolved to grade 0-1, up to 14 days.	1st appearance-Maintain dose-No change, 2nd appearance-Maintain dose No change, 3rd appearance - Resume 100% or dose reduce to 1000 mg/day, 4th appearance - Resume with a dose reduce to 1000 mg/day	1st appearance -Resume at 100%, 2nd appearance-Resume at 75% (rounded to nearest 150 mg), 3rd appearance-Resume at 50% of starting dose rounded to nearest 150 mg), 4th appearance-Discontinue permanently
Grade 3 except toxicity of cardiac ejection fraction and interstitial pneumonitis*	Both treatments- Interrupt until resolves to grade 0-1, up to 14 days.	Any appearance-Resume 100% or Reduce dose to 1000 mg permitted in consultation with GSK Medical Monitor.	1st appearance-Resume 75% of starting dose (rounded to nearest 150 mg), 2nd appearance-Resume 50% of starting dose (rounded to nearest 150 mg), 3rd appearance- Discontinue study treatment permanently
Grade 4 except 1st appearance of Toxicity of Cardiac Ejection Fraction and Interstitial pneumonitis*	Both treatments- Interrupt until resolves to grade 0-1.	Consult with GSK monitor to determine if in the best interest of the patient to continue at a dose reduction.	Consult GSK medical monitor to determine if it is in the best interest of the patient to continue at a dose level lower than the original capecitabine dose

* Subjects who have a >20% decrease in left ventricular cardiac ejection fraction (LVEF) from baseline, and the ejection fraction is below the institution's lower limit of normal, should have a repeat evaluation of ejection fraction 1-2 weeks later while still receiving GW572016. If the repeat ejection fraction evaluation confirms a >20% decrease in left ventricular cardiac ejection fraction, and the ejection fraction is below the institution's lower limit of normal, then GW572016 therapy should be temporarily discontinued. If the left ventricular ejection fraction recovers during the next 3 weeks, after consultation and approval of the GSK medical monitor, the subject may be restarted on GW572016 at a reduced dose. For such subjects, monitoring of left ventricular ejection fraction will then be performed 2 weeks and 4 weeks after re-challenge, and then every 4 weeks thereafter. If repeat ejection fraction evaluation still shows a decrease >20% in left ventricular ejection fraction from baseline, and the value is below the institution's lower limit of normal, then the subject should be withdrawn from GW572016 and capecitabine.

Source: Study EGF100151 original protocol.

Grading and dose modification for capecitabine specific toxicity, hand and foot syndrome (HFS) is as below. GW572016 should not be delayed due a grade 1-2 AE of hand/foot syndrome.

Table 70: Hand and Foot Toxicity Grade and dose modification

Criteria for grading palmar-plantar erthrodysthesis (hand and foot) syndrome following Capecitabine and dose modifications (Sifton, 2002)			
Toxicity Grade	Manifestations	During course of Therapy	Dose Adjustment for Next Cycle (% of starting dose rounded to nearest 150 mg tablet)
Grade 1	Numbness, dysesthesia/paresthesia, tingling, painless swelling, or erythema of the hands and/or feet that causes discomfort but does not disrupt normal activities of daily living	No interruption required	No change
Grade 2	Painful erythema and swelling of the hands and/or feet that results in discomfort affecting normal activities of daily living	Hold dose until resolve to Grade 0-1	Resume at 75%
Grade 3	Moist desquamation, ulceration, blistering, and severe pain of the hands and/or feet and/or severe discomfort that causes inability to work or perform activities of daily living	Discontinue permanently and discontinue from all study therapy	Discontinue permanently and discontinue from all study therapy

Source: Study EGF100151 original protocol.

Duration of treatment was to be dependent on the response to therapy. Subjects demonstrating a complete or partial response to therapy or have stable disease may continue on investigational therapy until disease progression or unacceptable toxicity. The study-defined treatment was to be terminated if the principle reason for ending treatment falls into one of the following categories:

- Disease progression;
- Adverse event (including intercurrent illness, unacceptable toxicity);
- Insufficient therapeutic effect (lack of efficacy/progressive disease);
- Deviation from protocol (including non-compliance);
- Lost to follow-up;
- Subject's own request for reasons other than those above.

Prohibited medications are as follows:

- Anti-cancer therapy should not be given until disease progression or withdrawal from study medication (GW572016 plus capecitabine or capecitabine). Subjects

who receive concurrent anti-cancer therapy (e.g., cytotoxic or biologic) will not be allowed to continue to receive treatment with study treatment (GW572016 plus capecitabine or capecitabine) therapy;

- Hormonal therapy
- Bisphosphonates initiated following study entry;

Reviewer: The bisphosphonates use initiated prior to study entry was allowed but not stratified for randomization.

- Any other investigational drugs from 30 days or 5 half lives, whichever is longer, prior to the first dose of study treatment (GW572016 plus capecitabine or capecitabine) until 28 days after the last dose of study treatment (GW572016 plus capecitabine or capecitabine) therapy;
- Oral or intravenous steroids (inhaled are permitted);
- GW572016 is predominately metabolized by CYP3A4. Medications that are either inducers or inhibitors of CYP3A4 are prohibited. Such as:
 - Antibiotics: clarithromycin, erythromycin, troleandomycin, ciprofloxacin, rifampin, norfloxacin, rifabutin
 - HIV Antivirals: delaviridine, indinavir, nelfinavir, ritonavir, saquinavir, efavirenz, nevirapine, amprenavir, lopinavir, sorivudine or its chemically related analogue such as brivudine
 - Anticonvulsants: phenytoin, carbamazepine, phenobarbital
 - Antidepressants: fluoxetine, nefazodone, fluvoxamine
 - Antifungals: itraconazole, ketoconazole, fluconazole, voriconazole
 - GI: antacids (within 1 hr before and after dosing), cimetidine
- Miscellaneous: glucocorticoids, amiodirone, diltiazem, pioglitazone, St. John's wort, grapefruit or its juice, rifabutin, mibefradil, diethyldithiocarbamate, gestodene, mifepristone, modafinil;
- The medications that contra-indicated with capecitabine: coumarin-derivative anticoagulant such as warfarin and phenprocoumon, leucovorin
- Miscellaneous drugs associated with 5-FU interactions: allopurinol, dipyridamole, folic acid, trimethoprim

In amendment 6, a table was added to further define wash-out period that required for prohibited CYP3A4 inhibitors and inducers:

Table 71: Study EGF 100151 prohibited CYP3A4 inhibitors and inducers

Drug Class	Agent	Wash-out ¹
CYP3A4 Inducers		
Antibiotics	all rifamycin class agents (e.g., rifampicin, rifabutin, rifapentine)	14 days
Anticonvulsants	phenytoin, carbamazepine, barbiturates (e.g., phenobarbital)	
Antiretrovirals	efavirenz, nevirapine	
Glucocorticoids (oral)	cortisone (>50 mg), hydrocortisone (>40 mg), prednisone (>10 mg), methylprednisolone (>8 mg), dexamethasone (>1.5 mg) ²	
Other	St. John's Wort, modafinil	
CYP3A4 Inhibitors		
Antibiotics	clarithromycin, erythromycin, troleandomycin	7 days
Antifungals	itraconazole, ketoconazole, fluconazole (>150 mg daily), voriconazole	
Antiretrovirals, Protease Inhibitors	delavirdine, nelfinavir, amprenavir, ritonavir, indinavir, saquinavir, lopinivir	
Calcium channel blockers	verapamil, diltiazem	
Antidepressants	nefazodone, fluvoxamine	
GI Agents	cimetidine, aprepitant	
Other	grapefruit, grapefruit juice	
	amiodarone	6 months
Miscellaneous		
Antacids	Mylanta, Maalox, Tums, Rennie's	1 hour before and after dosing
Herbal or dietary supplements	St. John's wort, modafinil	14 days

- At the time of screening, if a patient is receiving any of the above listed medications/substances, the medication or substance must be discontinued (if clinically appropriate) for the period of time specified prior to administration of the first dose of lapatinib and throughout the study period in order for the patient to be eligible to participate in the study.
- Glucocorticoid daily doses (oral) \leq 1.5 mg dexamethasone (or equivalent) are allowed. Glucocorticoid conversions are provided in parentheses.

10.1.1.1.6 Study Population

Approximately 372 female subjects (186 in each arm) with refractory advanced or metastatic breast cancer were to be enrolled. The study eligibility criteria were as follows:

Inclusion:

- Signed informed consent*
- Histologically or cytologically confirmed invasive breast cancer with stage IIIb or IV Disease*

3. *Documentation of ErbB2 overexpression (IHC 3+ or IHC 2+ with FISH confirmation) is required based on local laboratory or initial diagnostic results. Where testing is not feasible, central laboratory testing were to be utilized*
4. *Subjects must have documented progressive advanced or metastatic breast cancer. Progression for entry is defined as appearance of any new lesion not previously identified or increase of 25% or more in existent lesions and must be documented*
5. *Subjects must have refractory breast cancer defined as progression in the metastatic setting or relapse within 6 months of completing adjuvant therapy which must include:*
 - *At least 4 cycles of both anthracycline- and taxane-containing regimens (concurrently or sequentially)*
 - Or*
 - *At least 2 cycles, provided disease progression occurred while on the respective anthracycline- or taxane-containing chemotherapy regimen(s)*
 - *Subjects who relapse > 6 months after completion of adjuvant anthracycline containing chemotherapy, and for whom further anthracycline is not indicated, are eligible for the study if the remaining inclusion criteria are met.*
 - *Prior treatment with capecitabine is not permitted*
6. *Where eligible, prior treatment must have contain trastuzumab (Herceptin) alone or in combination with other chemotherapy for at least 6 weeks of standard doses*
7. *Subjects with hormone receptor positive tumors, must have disease progression following hormonal therapy*
8. *Female subjects must be ≥ 18 years of age*
9. *ECOG Performance Status of 0 or 1*
10. *Measurable disease according to RECIST (Response Evaluation Criteria in Solid Tumors)*
11. *Subjects must have archived tumor tissue available to re-evaluate intra-tumoral expression levels of ErbB1 and ErbB2 by IHC and FISH testing performed by the study central laboratory. Central laboratory results will not be used to determine subject eligibility for the study, unless testing is being used for required documentation of ErbB2 overexpression.*
12. *Life expectancy of ≥ 12 weeks*
13. *Subjects must have recovered from clinically significant side effects associated with prior radiotherapy and chemotherapy*

14. Measurable lesions may be in the field of prior adjuvant irradiation. However, there must be at least an 8-week period between the last radiation treatment and the baseline scan documenting disease status for the lesion to be measurable
15. Bisphosphonates should not be initiated following study entry
16. Cardiac ejection fraction within the institutional range of normal as measured by echocardiogram (MUGA scan may be performed if ECHO is not available)
17. Able to swallow and retain oral medication
18. Subjects must complete all screening assessments as outlined in the protocol
19. No prior systemic investigational drugs within the past 30 days or 5 half lives which ever is longer; topical investigational drugs within the past 7 days
20. Adequate Renal Function defined as a Creatinine Clearance $\geq 50\text{mL/min}$, determined by calculated creatinine clearance using Cockcroft and Gault Method and normalized to Body Surface Area (BSA)
21. Adequate hematological and hepatic function as defined in table below:

Table 72: Adequate function definitions

System	Laboratory Values
Hematologic	
ANC (absolute neutrophil count)	$\geq 1.5 \times 10^9/\text{L}$
Hemoglobin	$\geq 9 \text{ g/dL}$ (after transfusion if needed)
Platelets	$\geq 100 \times 10^9/\text{L}$
Hepatic	
Albumin	$\geq 2.5 \text{ g/dL}$
Serum bilirubin	$\leq 1.5 \times \text{ULN}$ unless due to Gilbert's Syndrome
AST and ALT	$\leq 3 \times \text{ULN}$ without liver metastases $\leq 5 \times \text{ULN}$ if documented liver metastases

Source: Original protocol of study EGF100151.

Amendment 5, Dec 3, 2004, the protocol revised inclusion criteria to require all subjects must to have had prior treatment with trastuzumab. Prior to this amendment subjects were required to have received trastuzumab unless local label requirements indicated they were not eligible for trastuzumab treatment.

Reviewer note: This change only affected a small portion of patients (2%, see prior therapy), there was only one patient who did not have trastuzumab after to this amendment (see protocol deviation).

Exclusion:

1. *Pregnant, or lactating females*
2. *Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel. In addition subjects with ulcerative colitis are also excluded*
3. *History of other malignancy. Subjects who have been disease-free for 5 years or subjects with a history of completely resected non-melanoma skin cancer or successfully treated in situ carcinoma are eligible*
4. *Concurrent disease or condition that would make the subject inappropriate for study participation, or any serious medical disorder that would interfere with the subject's safety*
5. *Unresolved or unstable, serious toxicity from prior administration of another investigational drug*
6. *Active or uncontrolled infection*
7. *Dementia, altered mental status, or any psychiatric condition that would prohibit the understanding or rendering of informed consent*
8. *Known history of uncontrolled or symptomatic angina, arrhythmia or congestive heart failure*
9. *Subjects taking coumarin-derivative anticoagulants such as warfarin and phenprocoumon*
10. *Known history of or clinical evidence of central nervous system (CNS) metastases or leptomeningeal carcinomatosis*
11. *Concurrent anti-cancer therapy (chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, or tumor embolization) other than capecitabine*
12. *Concurrent treatment with oral or intravenous [IV] steroids*
13. *Concurrent treatment with an investigational agent or participation in another clinical trial*

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14. Use of an investigational drug within 30 days or 5 half-lives, whichever is longer, preceding the first dose of in the study

15. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to GW572016 or excipients of GW572016

16. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to capecitabine, fluorouracil or any excipients

17. Known dihydropyrimidine dehydrogenase (DPD) deficiency

Amendment 2, May 24, 2004, revised exclusion to allow subjects with stable CNS metastasis (asymptomatic and off systemic steroids and anticonvulsants for at least 3 months) into the study.

Reviewer: This amendment was based on sponsor's preliminary data of observed CNS tumor responses in a single arm lapatinib study in patients with CNS metastatic breast cancer.

10.1.1.1.7 Study Monitoring

The safety and efficacy monitoring are listed as below:

Procedures	Screening	Day 1 Pre-Dose	Weeks 1,2,3	Every 3 Weeks	Every 6 Wks, for 24 wks	Every 12 wks, begin wk 24	Withdrawal Treatment/ Study Conclusion
Informed Consent	✓						
Archived Tumor Tissue for Biomarkers ¹	✓						
Inclusion/Exclusion Criteria	✓	✓					
Medical, Surgical & Treatment history ²	✓						
Physical Exam(Vital Signs, Weight, Height) ³	✓	✓	✓ ¹²		✓	✓	✓
ECOG Performance Status	✓	✓			✓	✓	✓
Echocardiogram ⁴	✓				✓	✓	✓
12 lead Electrocardiogram	✓						✓
AE / Toxicity Assessment ⁵	✓	✓	✓		✓	✓	✓
Record Concomitant Medications	✓	✓				✓	✓
Tumor Measurement (CT, MRI, Bone Scan) ⁶	✓				✓	✓	✓ ¹³
Serum Assay for ErbB1 and ErbB2	✓				✓	✓	✓
Hematology & Chemistry ⁷	✓	✓ ¹¹	✓ ¹²	✓ ¹²	✓	✓	✓
Calculate Creatinine Clearance ⁸	✓				✓	✓	✓
Serum Pregnancy Test	✓						
FACT B and EQ-5D		✓			✓	✓	✓
Pharmacogenetic Sample Collection ⁹	✓						
Dispense Investigational Agent ¹⁰		✓			✓	✓	
Ascertain Investigational Agent Compliance			✓		✓	✓	✓
Survival Assessment							✓ ¹⁴

1. Obtain archived tumor tissue for biomarker analysis.
2. Medical and surgical history to include evaluation of baseline signs and symptoms record in the CRF with the assigned NCI CTCAE grade on the appropriate page(s).
3. Height to be measured only at baseline.
4. Copies of ECHO (if the ECHO was inconclusive or are not performed at the institution, a MUGA scan should be done) performed on subjects who experience a >20% decrease in left ventricular cardiac ejection

fraction from baseline, and cardiac ejection fraction is below the institution's lower limit of normal, were to be required by GSK for review by an independent board.

5. Subjects were to be monitored at each scheduled assessment at the site, at any contact with the subject during the study, at withdrawal, and at the post-study follow-up visit for the occurrence of AEs/SAEs.
 6. A Bone scan were to be required at baseline. If the patient has bone metastases, a bone scan were to be repeated every 12-weeks. Otherwise bone scans were to be performed only if clinically indicated. If bone scan is equivocal, then correlative imaging is required
 7. Hematology evaluation will include hemoglobin, hematocrit, and red blood cell count, white blood cell count with differential and platelet count. Chemistry evaluation to include: sodium, potassium, chloride, bicarbonate, calcium, glucose, BUN or urea, uric acid, creatinine, AST, ALT, alkaline phosphatase, total bilirubin, total protein, and albumin.
 8. Calculated creatinine clearance must be ≥ 50 mL/min (be Cockcroft and Gault Method and normalized to BSA) to be enrolled.
 9. For subjects who consent to participate in pharmacogenetics research, a 10 mL blood sample was to be drawn. This sample can be drawn at any time during the study, however it is preferred that it be drawn at the first visit.
 10. A 6-week supply of GW572016 was to be dispensed to the subject.
 11. Review screening laboratory results. Any result outside the normal range was to be repeated (prior to the first dose) at investigator discretion.
 12. At week 1 and week 2, Hematology (CBC only) is required. At week 3, Hematology (CBC only) and Physical Exam with AE assessment is required. Additional tests should be performed when clinically indicated.
 13. If a subject withdraws for reason other than progression, tumor assessments are to be completed every 12 weeks until progression.
 14. Survival Assessments are to be completed every 12 weeks after discontinuation of study therapy.
- Source: Study EGF100151 original protocol.

10.1.1.1.8 Efficacy Assessment

The primary efficacy endpoint was time to progression (TTP), which defined as *the interval between the date of randomization and the earliest date of disease progression*.

Disease progression was to be determined for each subject according to definitions established in the response evaluation criteria in solid tumors (RECIST). Any subject who received at least 1 dose of GW572016 plus capecitabine or capecitabine alone, were to be considered eligible for response to treatment.

The protocol also includes the following condition as TTP events:

- *Treatment discontinuation with documented evidence of clinical deterioration due to breast cancer.*
- *Death due to breast cancer or of unknown cause (with documented evidence of clinical deterioration due to breast cancer) while receiving treatment.*

Reviewer: The original proposed TTP events included radiological disease progression, symptomatic disease progression, and death. Therefore, this actually is progression free survival. At the time of special protocol assessment, FDA recommended that the sponsor should use only radiological and death events for this primary endpoint measurement and exclude the symptomatic disease progression.

In response to FDA's recommendation from EOP2 meeting, the applicant had included following description in the original protocol: *GSK were to require copies of all radiological scans performed during the study for all subjects. If a subject discontinues from the investigational therapy before disease progression is noted, radiological scans done after discontinuation of investigational therapy should also be sent to GSK, until disease progression is confirmed. On receipt, GSK were to arrange for the independent, blinded review of all radiological scans to verify or question the qualitative nature of the apparent response. For subjects with skin lesions, all photographs will be sent for independent, blinded review as well.*

Reviewer: The use of a central and blinded radiological review and blinded review of radiological scans and/or medical photographs reduces the bias from an investigator's assessment.

10.1.1.1.9 Radiological Assessment Guidelines

Measurable lesion: Lesions that can be accurately measured in at least 1 dimension (longest diameter) of:

- 15 mm with conventional techniques (medical photograph [skin or oral lesion], palpation, plain X-ray, CT, or MRI). In the case of CT, the minimum size of a measurable lesion must be at least double the reconstruction interval (e.g., if the reconstruction interval is 10 mm, a measurable lesion must be 20 mm)

OR

- > 10 mm with spiral CT scan

Non-measurable lesion: All other lesions including lesions too small to be considered measurable including bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusions, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses not confirmed and followed by imaging techniques, cystic lesions, or disease documented by indirect evidence only (e.g., by laboratory values).

Response Criteria

Definitions for assessments of response for target lesion(s) and non-target lesions were as table below:

Table 73: Definitions for assessments of response for target lesion(s) and non-target lesions (RECIST)

Evaluation	Target Lesions	Non-Target Lesions
Complete Response (CR)	Disappearance of all target lesions.	disappearance of all non-target lesions
Partial Response (PR)	at least a 30% decrease in the sum of the LD of the target lesions, taking as a reference, the baseline sum LD.	n/a
Incomplete Response	n/a	Persistence of 1 or more non-target lesion(s).
Stable Disease (SD)	Neither sufficient shrinkage to qualify for a PR nor sufficient increase to qualify for progressive disease (PD), taking as reference, the smallest sum LD since the treatment started.	n/a
Progressive Disease	At least a 20% increase in the sum of the LD of target lesions, taking as reference, the smallest sum LD recorded since the treatment started, or the appearance of 1 or more new lesions.	Appearance of 1 or more new lesions and/or unequivocal progression of existing non-target lesions, and confirmed later by the independent radiologic reviewer.
Not Evaluable (NE)	Any subject who cannot be classified by 1 of the 4 preceding definitions.	n/a

Source: Study EGF 100151 original protocol

Best Overall Response

The best overall response was described as *the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD, the smallest measurements recorded since the treatment started). In general, the subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.*

Table 74: Evaluation of Best Overall Response (RECIST)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note:

- *Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.*
- *In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response criteria.*

Reviewer: The note above indicated the possible existence of symptomatic disease progression event in the study EGF100151.

Confirmation Criteria

- For claiming a PR or CR, a confirmatory disease assessment should be performed no less than 4 weeks after the criteria for response are first met. This should include a bone scan to document that progression of tumor bone lesions or appearance of new bone lesions have not occurred. If bone scans lesion(s) are equivocal, correlative imaging (i.e. plain film, CT, or MRI) is required to demonstrate malignant characteristics of lesions.
- To be assigned a status of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 4 weeks.

Reviewer: The confirmation requirement is consistent with RECIST.

10.1.1.1.10 Health Outcomes

Quality life (QOL) was to be assessed using the Functional Assessment of Cancer Therapy- Breast (FACT-B) questionnaire (version 4, 1997). It is a 36-item (27 general questions and 9 breast cancer specific questions) self-reporting instrument consisting of 5 dimensions: physical well-being, social/family well-being, emotional well-being, functional well-being, and a breast cancer subscale. Higher scores on the FACT-B scales indicate a higher quality of life.

10.1.1.1.11 Statistical Plan

Analysis Populations

The **Intent-to-Treat (ITT) population** was to comprise all randomized subjects who receive at least one dose of randomized therapy, and were to be used for the analysis of efficacy data.

Amendment 2, May 24, 2004, as per FDA recommendation, the protocol revised ITT population to all randomized subjects.

Reviewer: For the primary efficacy analyses of this NDA, the ITT population (all randomized) was used all randomized subjects regardless of whether they received any protocol treatment.

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

Reviewer: The applicant used patient actual treatment received as SP for the safety analyses in this report, since 16 patients received treatment that they were not assigned to, due to a technical transmission error.

The **Per-Protocol (PP) population** will comprise all randomized and treated subjects who comply closely with the protocol. Major protocol violations that would exclude subjects from the PP population were to be defined and documented in the Reporting and Analysis Plan (RAP) prior to breaking the blind. The PP population was to be used to provide a supplementary analysis of time to progression only.

Data Management

Withdrawal: Subjects were to be treated until disease progression or withdrawal from the study treatment due to unacceptable toxicity. Subjects may also withdraw from the study treatment or other reasons prior to disease progression or unacceptable toxicity. All

withdrawals were to be included in analyses up to the time of withdrawal. Subjects who are withdrawn prematurely from investigational product, but who are not withdrawn from the study at the same time, were to be included in all analyses regardless of the duration of treatment.

Missing Data: As the period of treatment for any subject were to be dependent on its efficacy and toxicity, the duration of follow-up will vary between subjects. Consequently, there were to be no imputation for missing data. Where appropriate, available data were to be summarized over specified intervals (e.g. from randomization until withdrawal from the study) by using suitable summary statistics. For time-to-event endpoints, the last date of known contact was to be used for those subjects who have not reached the event at the time of the analysis; such subjects were to be considered censored in the analysis.

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

Analyses

The single treatment comparison was to be between GW572016 plus capecitabine and capecitabine alone. Unless otherwise stated, all comparisons were to be performed using the ITT population. With planned enrollment of 372 subjects, there were to be will be a maximum of two data looks (one interim analyses and a final analysis) that were to occur at approximately equally spaced numbers of events: 133 and 266 events. O'Brien-Fleming stopping boundaries with one-sided 2.5% significance level were to be used to reject either H_0 (i.e. support for superior efficacy in the GW572016 + capecitabine arm) or H_A (i.e. support for inferiority or futility).

Amendment 5, Dec 3, 2004, the sample size increased from 372 to 528 to power the study for the secondary endpoint of overall survival. The amendment also added a second interim analysis and redefined the time of final analysis. The first interim analysis of TTP was unchanged, at 133 events. If the first analysis of TTP does not lead to early termination of the study for futility, then the study will continue to a second analysis of TTP at 266 events. If this second analysis of TTP provides support for the superiority of GW572016 plus capecitabine, then the study will continue to recruit approximately 528 subjects. When 457 deaths have been observed, an additional analysis of the secondary endpoint of overall survival will be performed on the mature survival data. The study will have 80% power to detect a 30% increase in median survival time in subjects who receive GW572016 + capecitabine (10.4 months) compared to subjects who receive capecitabine alone (8 months).

Reviewer: This amendment was reviewed and accepted by FDA.

Time to progression (TTP) was defined as *the interval between the date of randomization and the earliest date of disease progression*. The disease progression included either *treatment discontinuation with documented evidence of clinical deterioration due to the breast cancer*, or *Death due to breast cancer or of unknown cause (with documented evidence of clinical deterioration due to breast cancer) while receiving treatment*. For subjects who do not progress, time to progression was to be censored at the time of initiation of alternative anti-cancer therapy or time of last contact, if sooner.

Reviewer: The death of “unknown cause (with documented evidence of clinical deterioration due to breast cancer) while receiving treatment” could introduce uninterruptible data into the TTP analysis.

The times to progression were to be summarized using Kaplan-Meier survival curves, and compared between treatment arms using a stratified log-rank test. The primary population for this analysis was to be the ITT population, but the PP population was to be used additionally at the time of final analysis.

Overall Tumor Response Rate was defined as the percentage of subjects achieving either a complete (CR) or partial (PR) tumor response. The response rate was to be calculated from the independent review of best response which records confirmed cases of PR and CR only. Subjects with unknown or missing response were to be treated as non-responders who included in the denominator when calculating the percentage. Response rates were to be compared between treatment arms using stratified Fisher's exact tests. Approximate 95% confidence limits for the difference in response rates were to be calculated. Exact 95% confidence limits for the tumor response rates in each arm will also be calculated

Clinical Benefit: *Additional evidence for efficacy is provided by a measure of clinical benefit: the percentage of subjects with evidence of complete or partial tumor response or stable disease for at least 6 months. This was to be calculated for each treatment arm, and analyzed as described in the previous section.*

Time to Response was defined as “the time from randomization until first documented evidence of partial or complete tumor response (whichever status is recorded first)”. The analysis was to be based on responses confirmed at a repeat assessment, with the time to response taken as the first time the response was observed. The times to response were to be analyzed using a competing risk approach. A competing risk is the occurrence of a secondary event that precludes the possibility of the primary event occurring; death without response is a competing risk for time to response. The times to response were to be summarized using cumulative incidence curves that provide unbiased estimates of the cumulative probabilities of achieving a response, adjusted for deaths without a response. For subjects who withdraw with no tumor response, the time was to be censored at the time of withdrawal from the study. The times to response were to be compared between treatment arms using a stratified log-rank test.

Duration of Response was designed for subjects who show CR or PR, duration of response is defined to be *the time from first documented evidence of PR or CR until the first documented sign of disease progression*. For subjects who did not progress, duration was to be censored at the time of initiation of alternative anti-cancer therapy or time of last contact, if sooner. Duration of response was to be summarized using Kaplan-Meier survival curves. The median duration of response, first and third quartiles were to be presented with 95% confidence intervals.

Six-Month Progression-Free Survival (PFS) was the percentages of surviving subjects who are progression-free six months after the start of treatment were to be estimated from the Kaplan-Meier survival curves. Approximately 95% confidence limits were to be calculated, based on Greenwood's formula for the standard error of the Kaplan-Meier estimate.

Reviewer:

- The original six-month PFS analysis design was based on the sample size.
- A single time point time to event efficacy analysis does not take in to account the data present before and after the time point.
- In the protocol amendment 5, the applicant enlarged sample size from 372 to 528 to power the study with survival and add Kaplan-Meier PFS analysis.

Progression Free Survival (PFS): Amendment 5, Dec 3, 2004, a new section of PFS analysis was added to the protocol. The PFS was defined as *the time from randomization until the earliest date of disease progression or death to any cause, if sooner. Disease progression will be based on the assessments from the blind, independent review of objective evidence (e.g., radiological scans and medical photographs)*. For subjects who did not progress or die, PFS was to be censored at the time of last independently assessed radiological scan preceding the initiation of any alternative anti-cancer therapy. PFS was to be summarized using the Kaplan-Meier survival curves, and compared between treatment arms using a stratified log-rank test.

Overall Survival is defined as "the time from randomization until death due to any cause". For subjects who are still alive at the cut off date, time to death was to be censored at the time of last contact. Overall survival was to be summarized using Kaplan-Meier survival curves, and compared between treatment arms using a stratified log-rank test.

Safety Analyses will use the safety population the analysis of safety data.

Extent of Exposure: The numbers of subjects administered investigational product were to be summarized according to the duration of therapy.

Adverse Events (AEs) were to be coded using the standard GSK dictionary (MedDRA), and grouped by system organ class. They were to be summarized by frequency and

proportion of total patients, by system organ class and preferred term. Separate summaries were to be given for all AEs, for drug-related AEs, for serious AEs, and for AEs leading to withdrawal from the study.

The incidence of deaths will also be reported.

Clinical Laboratory Evaluations: Hematology, clinical chemistry, and urinalysis data were to be summarized at each scheduled assessment and presented by NCI CTCAE toxicity grade. The prevalence of values lying outside the reference range were also to be presented.

Other Safety Measures: The results of scheduled assessments of body weight, vital signs, 12-lead ECG, echocardiogram (MUGA scan may be performed if ECHO is not available), and ECOG performance status were to be summarized. Details were to be provided in the RAP.

Health Outcomes Analyses: The FACT-B questionnaire and EQ-5D questionnaire were to be completed on day 1 pre-dose, every 6 weeks for the first 24 weeks, followed by every 12 weeks and at withdrawal from randomized therapy. For the FACT-B, the following scores were to be calculated: total score, sub-scale scores, and a trial outcome index (TOI). TOI is the sum of the physical well-being, functional well-being and breast cancer sub-scale. Breast cancer sub-scale will also be presented to measure the symptom improvement. In addition, individual questions, which reflect symptoms of disease of particular interest, may be analyzed: nausea, shortness of breath, swollen arms, and pain. The EQ-5D is comprised of a 5-item health status measure and a visual analogue rating scale/feeling thermometer. These components are administered independently which results in the derivation of two utility measures. The first utility value were to be derived from the five domains of the EQ5-D in those countries where a scoring algorithm has been developed and the second utility value were to be derived from the feeling thermometer.

Biomarker(s) Analyses:

- Tumor tissue: 4 ErbB/EGFR family members (ErbB1, ErbB2, ErbB3, and ErbB4), AKT, MAPK, and potentially other biomarkers down stream of ErbB1 and ErbB2
- Serum ErbB1 and ErbB2 extracellular domains further details of the analysis of biomarkers were to be addressed in the RAP.

10.1.1.1.12 Independent Data Monitoring Committee (IDMC)

An IDMC was to be utilized during the conduct of this study. An IDMC is generally assembled when there are significant safety or efficacy issues that warrant external objective medical and/or statistical review in order to protect the ethical and safety

interests of subjects and to protect the scientific validity of the study. A copy of the IDMC charter is provided in this NDA submission.

STUDY RESULTS

10.1.1.2 Patient Demography and Characteristics

The study EGF100151 patient disposition were summarized at each cut off in section 6.1.4.1. Due to the protocol violations, such as incorrect treatment and other protocol deviations, the analysis populations were defined as ITT, SP and PPP, as described in section 6.1.4.1. There were total of 17 patients received incorrect treatment which was not they were randomized to (Apr 3 2006). The subject IDs of these patients are listed in table below. The reviewer verified this with the data sets that provided by the sponsor and noted that sponsor used patient's randomization assignment group for efficacy analyses and used patient's actual treatment group for safety analyses (see two tables below).

Table 75: Subjects received treatment opposes to their randomization assignment.

Investigator	Subject	Assigned Treatment	Actual Treatment Group
034246	619	Lapatinib1500mg + Capecitabine 2000mg/m ²	Capecitabine 2500mg/m ²
034753	117		
037298	1136		
040280	454		
044034	60		
044034	66		
044034	75		
044034	1409		
006342	332	Capecitabine 2500mg/m ²	Lapatinib 1500mg + Capecitabine 2000mg/m ²
029841	464		
033602	480		
034246	621		
037298	70		
040529	114		
043954	493		
043965	485		
060716	1161		

Source: EGF100151 study report.

Deviations of study EGF 100151 eligibility criteria are as below:

Table 76: Deviations of study EGF 100151 eligibility criteria

Deviation	Nov 15 2005 Cut-off		Apr 3 2006 Cut-off	
	LC N=163 (%)	C N=161 (%)	LC N=198 (%)	C N=201 (%)
Total	17 (10)	13 (8)	20 (10)	16 (8)
Received any prior anti-ErbB1/ErbB2 inhibitor other than trastuzumab	3 (2)	3 (2)	3 (2)	3 (1)
Inadequate hematological and hepatic function	5 (3)	0	6 (3)	0
Inadequate renal function	1 (<1)	3 (2)	1 (<1)	5 (2)
Non-measurable disease according to RECIST	3 (2)	0	4 (2)	0
Missing screening assessments	0	2 (1)	0	2 (<1)
No progression following hormonal therapy for hormone receptor positive tumors	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Cardiac ejection fraction outside normal range	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Clinically significant side effects associated with prior radio-/chemo-therapy still present	0	1 (<1)	0	1 (<1)
CNS metastases or unstable CNS metastases	0	1 (<1)	0	1 (<1)
Concurrent anti-cancer therapy other than capecitabine	0	1 (<1)	0	1 (<1)
Concurrent treatment with investigational agent	0	1 (<1)	0	1 (<1)
History of other malignancy	1 (<1)	0	1 (<1)	0
No documentation of ErbB2 overexpression	1 (<1)	0	1 (<1)	0
No documented progressive advanced or metastatic breast cancer	1 (<1)	0	1 (<1)	0
No refractory breast cancer defined as progression after prior therapy	1 (<1)	0	3 (2)	1 (<1)
Prior treatment did not contain trastuzumab for at least 6 weeks ¹	1 (<1)	0	1 (<1)	0

1. Subjects enrolled prior to protocol amendment 2, which require subjects must receive trastuzumab in order to be eligible for the study, were not classified as protocol violators. There were 3% subjects did not receive herceptin, 5 for each arm.

LC = Lapatinib + Capecitabine , C = Capecitabine alone

Source: Study EGF 100151 report.

Reviewer: As describe in tables above, the major deviations are serious violations in eligibility criteria, such as lack of prespecified prior therapy, Her-2 status, and no study treatment or incorrect treatment, or received other anticancer treatment while on study.

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

The reviewer verified and agreed with the sponsor's baseline demographic summary, as shown below.

Table 77: Study EGF 100151 subjects baseline demographic (ITT)

	Nov 15 2005 cut-off			Apr 3 2006 cut-off		
	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
Age, years						
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)
Age group, n (%)						
<65 years	138 (85)	142 (88)	280 (86)	165 (83)	177 (88)	342 (86)
>=65 yrs	25 (15)	19 (12)	44 (14)	33 (17)	24 (12)	57 (14)
Race, n (%)						
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)
Baseline disease stage						
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)
Number of metastatic sites						
>=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)			
Weeks since last trastuzumab administrated						
< 6 weeks	83 (53)	76 (49)		98 (50)	98 (50)	
6-12 weeks	28 (18)	35 (22)		37 (19)	38 (19)	
>12 weeks	46 (29)	43 (28)		61 (31)	58 (29)	
Missing	0 (0)	2 (1)		0 (0)	3 (2)	

Data Source: Study EGF 100151 report.

1. Safety population

Reviewer: The study subjects baseline characteristics appeared to be balanced between the two arms.

The reviewer verified and agreed with the sponsor's summary of disease characteristics and the site of metastasis, as shown below:

Table 78: Study EGF 100151 baseline disease characteristics (ITT, Nov 15 2005 cut-off)

	Lapatinib+ Capecitabine N=163 n (%)	Capecitabine N=161 n (%)	All Subjects N=324 n (%)
ErbB2 Overexpression Status			
Overexpressed	162 (>99)	161 (100)	323 (>99)
Not overexpressed	1 (<1)	0	1 (<1)
Histology at First Diagnosis			
Infiltrating duct NOS	133 (82)	141 (88)	274 (85)
Other	20 (12)	12 (7)	32 (10)
Lobular invasive	6 (4)	5 (3)	11 (3)
Tubular	2 (1)	1 (<1)	3 (<1)
Mucinous	1 (<1)	1 (<1)	2 (<1)
Adenocystic	0	1 (<1)	1 (<1)
Papillary	1 (<1)	0	1 (<1)
Disease Stage at First Diagnosis			
	11 (7)	20 (12)	31 (10)
	73 (45)	68 (42)	141 (44)
III	60 (37)	57 (35)	117 (36)
IV	19 (12)	16 (10)	35 (11)
Baseline Disease Stage			
Stage IV – visceral	116 (71)	118 (73)	234 (72)
Stage IV – non-visceral	40 (25)	36 (22)	76 (23)
Stage IIIb or IIIc with T4 lesion	7 (4)	7 (4)	14 (4)
Local Recurrence after Surgery			
N	148	151	299
Yes	42 (28)	48 (32)	90 (30)
No	105 (71)	103 (68)	208 (70)
Unknown	1 (<1)	0	1 (<1)
Receptor Status¹			
ER- / Pr-	80 (49)	80 (50)	160 (49)
ER+ / Pr+	38 (23)	37 (23)	75 (23)
ER+ / Pr-	14 (9)	22 (14)	36 (11)
ER+ / Pr unknown	14 (9)	8 (5)	22 (7)
ER- / Pr+	12 (7)	8 (5)	20 (6)
ER- / Pr unknown	4 (2)	5 (3)	9 (3)
ER unknown / Pr unknown	1 (<1)	1 (<1)	2 (<1)

Source: Study EGF 100151 report.

Table 79: EGF 100151 baseline disease characteristics (ITT, Ape 3 2006 cut-off)

	Lapatinib+ Capecitabine N=198 n (%)	Capecitabine N=201 n (%)	All Subjects N=399 n (%)
ErbB2 Overexpression Status¹			
Overexpressed	197 (>99)	201 (100)	398 (>99)
Not overexpressed	1 (<1)	0	1 (<1)
Histology at First Diagnosis			
Infiltrating duct NOS	163 (82)	177 (88)	340 (85)
Other	23 (12)	13 (6)	36 (9)
Lobular invasive	8 (4)	8 (4)	16 (4)
Tubular	2 (1)	1 (<1)	3 (<1)
Mucinous	1 (<1)	1 (<1)	2 (<1)
Adenocystic	0	1 (<1)	1 (<1)
Papillary	1 (<1)	0	1 (<1)
Disease Stage at First Diagnosis			
I	15 (8)	22 (11)	37 (9)
II	85 (43)	91 (45)	176 (44)
III	74 (37)	65 (32)	139 (35)
IV	23 (12)	23 (11)	46 (12)
Unknown	1 (<1)	0	1 (<1)
Baseline Disease Stage			
Stage IV – visceral	148 (75)	158 (79)	306 (77)
Stage IV – non-visceral	43 (22)	35 (17)	78 (20)
Stage IIIb or IIIc with T4 lesion	7 (4)	8 (4)	15 (4)
Local Recurrence after Surgery			
n	181	188	369
Yes	51 (28)	59 (31)	110 (30)
No	129 (71)	129 (69)	258 (70)
Unknown	1 (<1)	0	1 (<1)
Receptor Status¹			
ER- / PR-	95 (48)	101 (50)	196 (49)
ER+ / PR+	49 (25)	48 (24)	97 (24)
ER+ / PR-	18 (9)	25 (12)	43 (11)
ER+ / PR unknown	16 (8)	10 (5)	26 (7)
ER- / PR+	13 (7)	10 (5)	23 (6)
ER- / PR unknown	4 (2)	6 (3)	10 (3)
ER unknown / PR unknown	3 (2)	1 (<1)	4 (1)

Source; Study EGF 100151 report.

Table 80: Study EGF 100151 subjects baseline metastatic disease sites (ITT, Nov 15 2005 cut-off)

	Lapatinib+ Capecitabine N=163 n (%)	Capecitabine N=161 n (%)	All Subjects N=324 n (%)
Number of Metastatic Sites			
≥3	79 (48)	80 (50)	159 (49)
2	53 (33)	46 (29)	99 (31)
1	31 (19)	34 (21)	65 (20)
0	0	1 (<1)	1 (<1)
Involved Sites			
Visceral ¹ and non-visceral	98 (60)	96 (60)	194 (60)
Non-visceral only (includes LABC)	38 (23)	36 (22)	74 (23)
Visceral ¹ only	27 (17)	28 (17)	55 (17)
No metastatic sites	0	1 (<1) ²	1 (<1)
Metastatic Disease Sites (≥5%)³			
Liver	83 (51)	76 (47)	159 (49)
Bone	73 (45)	81 (50)	154 (48)
Lung	77 (47)	68 (42)	145 (45)
Lymph nodes	62 (38)	70 (43)	132 (41)
Skin	31 (19)	32 (20)	63 (19)
Chest wall	26 (16)	23 (14)	49 (15)
Other	24 (15)	22 (14)	46 (14)
Breast	21 (13)	21 (13)	42 (13)
Pleura	17 (10)	22 (14)	39 (12)
Abdomen/viscera	12 (7)	18 (11)	30 (9)
CNS	5 (3)	13 (8)	18 (6)

1. Visceral sites include abdomen/viscera, adrenals, CNS, heart, liver, lung, pancreas, and stomach.
 2. Subject had chest wall disease based on independent review of lesion data.
 3. Subjects may have had more than one site of metastatic disease.
- Source: Study EGF 100151 report.

**APPEARS THIS WAY
 ON ORIGINAL**

Table 81: Study EGF 100151 subjects baseline metastatic disease sites (ITT, Apr 3 2006 cut-off)

	Lapatinib+Capecitabine N=198 n (%)	Capecitabine N=201 n (%)	All Subjects N=399 n (%)
Number of Metastatic Sites			
≥3	98 (49)	96 (48)	194 (49)
2	61 (31)	61 (30)	122 (31)
1	39 (20)	44 (22)	83 (21)
Involved Sites			
Visceral and non-visceral	120 (61)	122 (61)	242 (61)
Non-visceral only	45 (23)	43 (21)	88 (22)
Visceral ¹ only	33 (17)	36 (18)	69 (17)
Metastatic Disease Sites (≥5%)²			
Liver	107 (54)	101 (50)	208 (52)
Bone	92 (46)	95 (47)	187 (47)
Lung	90 (45)	86 (43)	176 (44)
Lymph nodes	80 (40)	88 (44)	168 (42)
Skin	37 (19)	41 (20)	78 (20)
Chest wall	31 (16)	29 (14)	60 (15)
Breast	26 (13)	26 (13)	52 (13)
Other	26 (13)	24 (12)	50 (13)
Pleura	18 (9)	25 (12)	43 (11)
Abdomen/visceral	14 (7)	21 (10)	35 (9)
CNS	8 (4)	15 (7)	23 (6)

1. Visceral sites include abdomen/viscera, adrenals, CNS, heart, liver, lung, pancreas, and stomach.

2. Subjects may have had more than one site of metastatic disease.

Source; Study EGF 100151 report.

Reviewer: The disease characteristics appear to be balanced between the two arms.

The reviewer verified and agrees with the sponsor's summary of previous anticancer treatment

**APPEARS THIS WAY
ON ORIGINAL**

Table 82: Study EGF 100151 subjects prior anticancer therapies (ITT, Nov 15 2005)

	Lapatinib+Capecitabine N=163 n (%)	Capecitabine N=161 n (%)
Any medication	159 (98)	159 (99)
All medications (taxane+anthracycline+trastuzumab)	156 (96)	145 (90)
Taxanes	159 (98)	156 (97)
Docetaxel	118 (72)	124 (77)
Paclitaxel	71 (44)	65 (40)
Anthracyclines	158 (97)	156 (97)
Doxorubicin hydrochloride	81 (50)	81 (50)
Epirubicin	47 (29)	46 (29)
Doxorubicin	30 (18)	31 (19)
Mitoxantrone	9 (6)	2 (1)
Epirubicin hydrochloride	5 (3)	5 (3)
Anthracyclines (not specified)	1 (<1)	1 (<1)
Trastuzumab¹	157 (96)	156 (97)
Hormonals	78 (48)	72 (45)
Tamoxifen	51 (31)	41 (25)
Anastrozole	26 (16)	24 (15)
Exemestane	19 (12)	18 (11)
Letrozole	19 (12)	17 (11)
Tamoxifen Citrate	16 (10)	15 (9)
Goserelin	4 (2)	10 (6)
Fulvestrant	5 (3)	8 (5)
Megestrol acetate	0	5 (3)
Leuprorelin acetate	1 (<1)	3 (2)
Triptorelin	1 (<1)	2 (1)
Toremifene	1 (<1)	1 (<1)

1. The protocol was amended to require subjects to receive trastuzumab in order to be eligible for the study.
 Source; Study EGF 100151 report.

**APPEARS THIS WAY
 ON ORIGINAL**

Table 83: Study EGF 100151 subjects prior anticancer therapies (ITT, Apr 4 2006)

ATC Category	Lapatinib+Capecitabine N=198 n (%)	Capecitabine N=201 n (%)
Any medication	198 (100)	201 (100)
All medications (taxane+anthracycline+trastuzumab)	191 (96)	188 (94)
Taxanes	198 (100)	199 (>99)
Docetaxel	143 (72)	154 (77)
Paclitaxel	93 (47)	83 (41)
Anthracyclines	194 (98)	199 (>99)
Doxorubicin hydrochloride	98 (49)	97 (48)
Epirubicin	61 (31)	63 (31)
Doxorubicin	35 (18)	41 (20)
Mitoxantrone	11 (6)	4 (2)
Epirubicin hydrochloride	5 (3)	8 (4)
Anthracyclines (not specified)	1 (<1)	1 (<1)
Trastuzumab	196 (99)	197 (98)
Trastuzumab	196 (99)	197 (98)
Hormonals	99 (50)	93 (46)
Tamoxifen	61 (31)	55 (27)
Anastrozole	36 (18)	33 (16)
Letrozole	24 (12)	28 (14)
Exemestane	25 (13)	23 (11)
Tamoxifen Citrate	22 (11)	19 (9)
Fulvestrant	12 (6)	8 (4)
Goserelin	6 (3)	12 (6)
Megestrol acetate	1 (<1)	5 (2)
Leuprorelin acetate	1 (<1)	4 (2)
Triptorelin	2 (1)	2 (<1)
Toremifene	1 (<1)	1 (<1)
Navelbine	93 (47)	92 (46)
Vinorelbine	92 (46)	92 (46)
Vinorelbine ditartrate	2 (1)	0
Gemcitabine	32 (16)	22 (11)
Gemcitabine	32 (16)	22 (11)

Source; Study EGF 100151 report.

**APPEARS THIS WAY
 ON ORIGINAL**

Table 84: Study EGF 100151 subjects prior trastuzumab treatment (ITT, Nov 15 2005 cut-off)

	Lapatinib+ Capecitabine N=163 n (%)	Capecitabine N=161 n (%)
Trastuzumab exposure, weeks		
n	157	156
Mean (SD) weeks	57.9 (49.75)	59.0 (50.16)
Median (min-max)	42.3 (3-296)	44.1 (5-329)
Intent of trastuzumab n (%)		
Adjuvant	7 (5)	9 (6)
Metastatic	150 (96)	146 (94)
Neo-adjuvant	0	1 (1)
Weeks since last trastuzumab administered		
Less than 6 weeks	83 (53)	76 (49)
6 - 12 weeks	28 (18)	35 (22)
More than 12 weeks	46 (29)	43 (28)
Missing	0	2 (1)
N	150	146
Progressed on/after trastuzumab treatment for metastatic cancer n (%)	148 (99)	142 (97)

Source: Study EGF 100151 report.

**APPEARS THIS WAY
ON ORIGINAL**

Table 85: Study EGF 100151 subjects prior trastuzumab treatment (Apr 3 2006 cut-off)

	Lapatinib+Capecitabine N=198 n (%)	Capecitabine N=201 n (%)
Trastuzumab exposure, weeks		
n	196	197
Mean (SD)	57.2 (48.19)	59.3 (49.28)
Median (min-max)	43.6 (3 - 296)	45.3 (0 - 329)
Intent of trastuzumab, n (%)		
Adjuvant	9 (5)	7 (4)
Metastatic	187 (95)	189 (96)
Neo-adjuvant	0	1 (1)
Weeks since last trastuzumab administered		
<6 weeks	98 (50)	98 (50)
6 - 12 weeks	37 (19)	38 (19)
>12 weeks	61 (31)	58 (29)
Missing	0	3 (2)
PD		
Progressed on/after trastuzumab treatment for metastatic cancer n (%)	182 (97)	185 (98)

Source; Study EGF 100151 report.

Reviewer: At the time of clinical up, date (Apr 3 2006) about 95% of the ITT population received all required prior therapies, and about 98% of patients received at least of one of a taxane, anthracycline or trastuzumab. The prior anticancer treatment, including the treatment duration and response status of trastuzumab, appears to be balanced between the two arms.

The data sets did not contain details of patients' baseline Her2 status (IHC 3+ vs. IHC 2+ with FISH confirmation), since this was recorded on a separate work sheet which was not part of the CRF. Upon FDA request, the applicant submitted Her2 baseline status summary based on the information collected from the investigator's worksheet as Apr 3 2006 cut-off date, as shown below. Not data set provided for verification.

Table 86: Study EGF 100151 subject baseline Her2 status (ITT, Apr 3 2006 cut-off)

Her 2 status \ Treatment arms	Randomized Treatment			Actual Treatment Received		
	LC N=198 (%)	C N=201 (%)	Total N = 399 (%)	LC N=198 (%)	C N=191 (%)	Total N = 389 (%)
Her2 Positive	189 (95)	190 (95)	388 (97)	189 (95)	182 (95)	371 (95)
IHC 3+	154 (78)	160 (80)	321 (80)	152 (77)	154 (81)	306 (79)
IHC2+ FISH	35 (17)	30 (15)	67 (18)	37 (18)	28 (14)	65 (16)

Source: additional data submitted by the applicant per reviewers' request.

LC = Lapatinib + capecitabine, C = capecitabine

Reviewer: This result is slightly different from the clinical up date (Apr 3 2006) data set that applicant generate from CRF. There were actually 11 subjects lack of protocol defined Her 2 status, but the applicant only reported one case of Her 2 negative the study report (Table 78 and 79). Therefore, the total number of Her 2 positive subjects randomized was actually 2% less (398 to 388) than the applicant claimed. However, 97% percent randomized subjects with protocol defined Her2 status is acceptable. No response observed in non-Her-2 overexpress breast cancer patients (see section 6.1.4.2.5).

The reviewer verified and agreed with the sponsor's summary of concomitant and concurrent medications during the study. Total subjects received concomitant and concurrent medications medication and medication that are significant to the efficacy (bone event as progression) and safety (pain and rash) results were included in the table below.

Table 87: Study EGF 100151 subjects concomitant and concurrent medications (ITT, Nov 15 2006 cut-off)

	Lapatinib + Capecitabine N=163 (%)	Capecitabine N=161 (%)
Concomitant medications (started prior to 1st dose of study medication)	116 (71)	120 (75)
Paracetamol	40 (25)	29 (18)
Zoledronic acid	22 (13)	20 (12)
Concurrent medications (started after 1st dose of study medication)	125 (77)	128 (80)
Loperamide hydrochloride	40 (25)	36 (22)
Paracetamol	37 (23)	36 (22)
Pyridoxine hydrochloride	17 (10)	9 (6)
Dexamethasone	9 (6)	16 (10)

Source: Study EGF 100151 report.

Reviewer: The concomitant and concurrent medications that were used for bone metastasis, pain or rash appeared to be balanced between the two arms, including concomitant bisphosphonates, which was stratified for neither the randomization nor the bone disease.

10.1.1.3 Efficacy

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

At interim analysis, 121 TTP events were identified by IRC in 324 subjects randomized at the cut off date. The IRC assessed TTP was statistically significant in favor of testing group, with a hazard ratio of 0.49 (95% CI: 0.34, 0.71, two-sided p-value = 0.00008). The

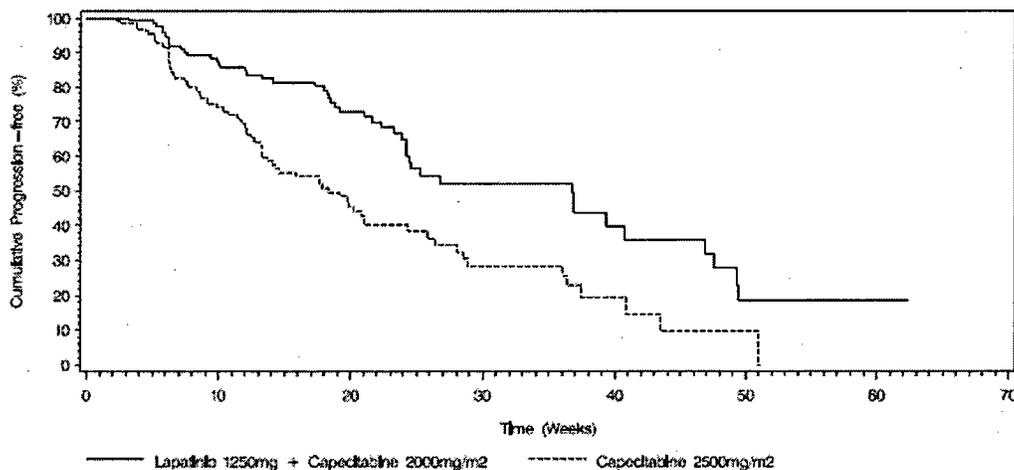
IRC assessed median TTP in the lapatinib + capecitabine group was 36.7 weeks compared to 19.1 weeks in the capecitabine group, a 17 weeks improvement. The O'Brien Fleming (Pamplona-Tsiatis implementation) boundary for 121 TTP events was $p \leq 0.0038$ (two-sided), as shown in Table and Figure below.

Table 88: Study EGF 100151 TTP interim analysis by IRC assessment (ITT, Nov 15 2005 cut-off)

	Lapatinib + Capecitabine N=163	Capecitabine N=161
Progression and death, n (%)		
Progressed or died due to breast cancer	49 (30)	72 (45)
Died due to cause other than breast cancer	0	4 (2)
Censored, follow-up ended	9 (6)	12 (7)
Censored, follow-up ongoing	105 (64)	73 (45)
Cumulative incidence estimate of TTP, weeks		
1 st Quartile	18.7	9.9
Median	36.7	19.1
3rd Quartile	49.3	37.4
Hazard ratio		
Estimate, [95% CI] ¹	0.49 [0.34, 0.71]	
Log-rank p-value ²	0.00008	

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

Figure 11: Study EGF 100151 TTP interim analysis by IRC assessment - Kaplan Meier Estimates (ITT, Nov 15 2005 cut-off)



Note: Four subjects who died due to causes other than breast cancer were censored.

The TTP analyses by IRC assessment in SP and PPP population were consistent with that of ITT and described in section 6.1.4.2.1.2.

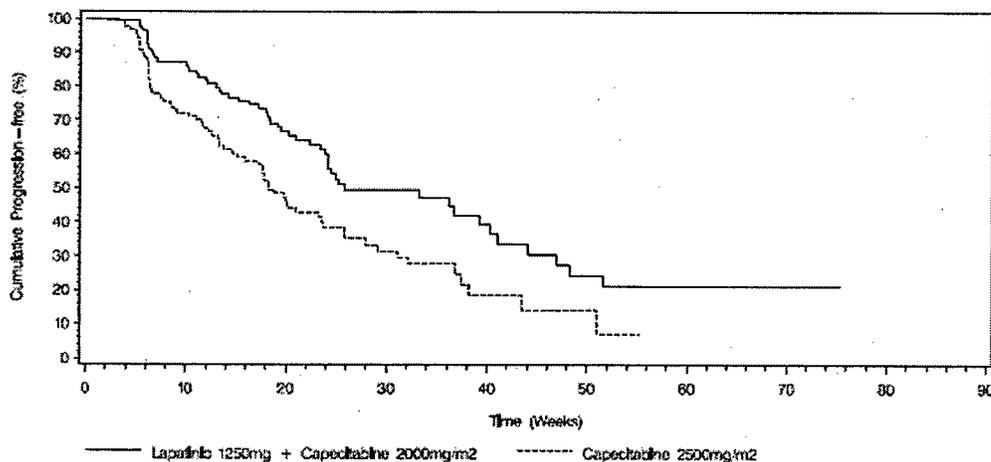
The interim analysis cut off date was determined at 133 event plus a additional 10% by the investigator's assessment to ensure that the independent review assessment for primary TTP analysis were to be conducted at approximately 133 events. Using this assessment, 7 weeks improvement of median TTP in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

Table 89: Study EGF 100151 TTP interim analysis by investigator assessment (ITT, Nov 15 2005 cut-off)

	Lapatinib + Capecitabine N=163 (%)	Capecitabine N=161 (%)
Progression and death, n (%)		
Progressed or died due to breast cancer	59 (36)	74 (46)
Died due to cause other than breast cancer	2 (1)	4 (2)
Censored, follow-up ended	8 (5)	12 (7)
Censored, follow-up ongoing	94 (58)	71 (44)
Cumulative incidence estimate of TTP, weeks		
1st Quartile	16.3	8.4
Median	25.9	18.9
3rd Quartile	51.6	37.4
Hazard ratio		
Estimate, [95% CI] ¹	0.59 [0.42, 0.84]	
Log-rank p-value ²	0.00219	

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

Table 90: Study EGF 100151 TTP interim analysis by investigator assessment - Kaplan Meier Estimates (ITT, Nov 15 2005 cut-off)



Note: Four subjects in capecitabine group and two subjects in lapatinib + capecitabine who died due to causes other than breast cancer were censored due to TTP definition.

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For the difference in TTP improvement between the IRC and investigators assessment, the applicant analyzed disagreement between the two assessments for TTP analysis of study EGF100151. The reviewer reviewed these data and agreed with the applicant analyses, as summarized in two tables below.

The discordance of independent review and investigator assessment were discussed in section 6.1.4.2.1.1. This reviewer selected 15 representative cases for Imaging consultants review and recommendation, as listed below. The imaging consultants' input was summarized in section 6.1.4.2.1.

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Table 91: Study EGF 100151 TTP events and duration difference between INV and IRC assessment

INVID	Subject	Arm	Difference (IRC-INV, days)	IRC TTP (days)	INV TTP (days)	Applicant Explanation
33988	651	1	4	7	7	IRC followed: T=5 liver by spiral CT & NT=CNS, liver by spiral CT and bone by nuclear scan. INV followed: T=2 liver by spiral CT & NT=liver by spiral CT and 5 CNS by MRI. IRC TTP =date of death. INV observed PD 15JUL05 due to symptomatic progression and recorded PD 15JUL05 and then subject died on INV symptomatic PD)
43965	485	2	105			IRC followed: T=liver by spiral CT & NT=none. INV followed: T=2 chest wall and trapezius mass by MRI & NT= skin by direct measure. IRC observed PD 08DEC04 due to new lymph node by MRI. IRC oncologist overruled the IRC radiologist for PD by new lymph node and did not observe PD until 17AUG05. INV observed PD 04MAY05 due to new brain lesion; however subject did not withdrawn from IP until 20JUN05.
40179	413	2	65			IRC followed: T=liver by spiral CT & NT=bone by nuclear scan. INV followed: T=2 liver by spiral CT and NT=bone by x-ray and bone by nuclear scan. IRC TTP =date of death. INV observed PD 17JAN05 due to new liver lesion by spiral CT and new bone lesion by x-ray.
014344	761*	2	65			IRC followed: T=none & NT=none. INV followed: T=2 chestwall by direct measure & NT=none. IRC observed PD 10NOV05 due to new CNS lesion. INV observed PD 08NOV05 due to new skin lesion by direct measure; however this PD occurred after the date of 133 rd PD and therefore censored by analysis. IRC received photos from 08NOV05.
040529	113*	1	-34			IRC followed 2 lung by spiral CT & NT=liver by spiral CT. INV followed: T=NONE & NT=liver by spiral CT, 4 bone by spiral CT. IRC observed PD 03AUG05 due to new lung lesion, worsening lung lesion and increase in target lesions. INV observed PD 12OCT05 due to new CNS (cerebellum); however this PD occurred after the date of 133 rd PD and therefore censored by analysis.
040529	128*	1	-29			IRC followed: T=lymph nodes by spiral CT & NT=pleura by spiral CT. INV followed: T=3 lymph nodes by spiral CT. IRC observed PD 14DEC04 due to worsening non-target pleura. INV subject died due to a serious adverse event considered a competing risk.
043954	490*	1	36			IRC followed: T=3 liver by spiral CT & NT=liver by spiral CT and bone by nuclear scan. INV followed: T=2 liver by spiral CT & NT=2 liver and lung by spiral CT and bone by nuclear scan. IRC observed PD 15OCT04 due to new CNS lesions by spiral CT. INV observed PD 07SEP05 due to an increase in target lesions. However, the subject continued to receive IP and imaging until INV observed PD 13OCT04 due to new spine lesions by MRI and 15OCT04 new CNS (intra cranium) by spiral CT.
043954	1115*	2	7			IRC followed: T= none (missing baseline photos) & NT= bone by spiral CT. INV followed: T=chest wall by direct measure & NT=chest wall and lymph nodes by direct measure. INV observed PD 19APR05 due to new skin lesions by direct measure.
043954	1118*	2	0			IRC followed: T=none & NT=liver and pleura by spiral CT. INV followed: T=2 liver by spiral CT & NT=liver and lung by spiral CT. INV observed PD on 15MAR05 due to increase in target lesions and worsening of non-target lesions.
068711	691*	2	-47			IRC followed: T=liver by spiral CT & NT=liver by spiral CT. INV followed: T=liver by spiral CT &

INVID	Subject	Arm	Difference (IRC-INV, days)	IRC TTP (days)	INV TTP (days)	Applicant Explanation
						NT=lung by spiral CT. IRC observed PD 06JUL05 due to increase in target lesions. INV observed PD 22AUG05 due to increase in target lesion; however subject was not withdrawn from IP until 08SEP05 and INV observed PD 10SEP05 due to new brain lesions by spiral CT.
001431	403	1	169			IRC followed: T=4 liver lesions by spiral CT & NT=bone by nuclear scan and lymph node by spiral CT. INV followed: T=4 liver lesions by spiral CT & NT=bone by spiral CT. IRC TTP ~ -date of death. INV observed PD 26MAY05 due to new liver lesion.
002410	61	1	79			IRC followed: T=4 liver lesions by spiral CT & NT=bone by nuclear scan and lymph node by spiral CT. INV followed: T=4 liver lesions by spiral CT & NT=bone by spiral CT. IRC TTP ~ -date of death. INV observed PD 26MAY05 due to new liver lesion.
005117	325	1	123			IRC followed: T=none & NT=pleura and "around spleen" by MRI and bone by nuclear scan. INV observed: T=liver by MRI & NT=liver and ascites by MRI. IRC did not receive any scans after INV observed PD. IRC TTP ~ -date of death. The INV observed PD 21MAR05 due to progressive ascites non target.
034749	122	1	37			IRC followed: T=2 lymph nodes and 3 liver by spiral CT & NT=liver and lymph nodes by spiral CT. INV followed: T=3 liver by spiral CT & NT=lung by spiral CT. IRC TTP ~ -date of death. INV observed PD 16MAY05 due to increase in target lesions.
036185	615	1	-40			IRC followed: T=2 lymph nodes and cul-de-sac by spiral CT & NT=lymph node by spiral CT and bone by nuclear scan. INV followed T=2 lymph nodes and 2 liver by spiral CT & NT=bone by nuclear scan. IRC observed PD 01JUL05 due to increase in target lesion. INV observed PD 10AUG05 due to new bone lesions.
43133	47	1	94			IRC followed: T= 4 lymph nodes by spiral CT & NT= lymph node and lung by spiral CT. INV followed: T= lung, 2 lymph nodes by spiral CT & NT= none. IRC TTP ~ -date of death. INV observed PD 04JUL05 due to increase of target lesions.
54788	50	1	104			IRC followed: T=lymph node by spiral CT & NT=lymph node by spiral CT. INV followed: T=lymph node by spiral CT & NT=none. IRC TTP ~ -date of death. INV observed PD 20JAN05 due to increase in target lesion by spiral CT.
57051	831	1	125			IRC followed: T= breast and 2 liver by spiral CT & NT=liver by spiral CT and bone by nuclear scan. INV followed: T=2 liver by spiral CT & NT= lung, bone, and 2 liver all by spiral CT. IRC observed PD 07MAR05 due to increase in target lesions and worsening liver nontarget lesion. INV observed PD 02NOV04 due to worsening liver nontarget lesion. Subject started IP on 22SEP04 and ended IP on 09MAR05 and scans were sent to IRC during the time that subject received IP.
58148	799	1	127			IRC followed: T=3 liver by spiral CT & NT=lung and liver by spiral CT. INV followed: T=5 liver and 2 lung by spiral CT & NT = none. IRC TTP ~ -date of death. INV observed PD 03/JAN05 due to new liver lesion by spiral CT.
27231	710	2	20			IRC followed: T=lymph node, chestwall, and liver by spiral CT & NT=pleura and liver by spiral CT. INV followed: T=4 chest wall, lymph node, and liver by spiral CT & NT=pleura and lung by spiral CT. IRC TTP ~ -death date. INV observed PD 06SEP05 due to new liver lesions by spiral CT.
034749	121	2	43			IRC followed: T=2 liver and breast by spiral CT & NT=lymph nodes by spiral CT. INV followed: T=2

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INVID	Subject	Arm	Difference (IRC-INV, days)	IRC TTP (days)	INV TTP (days)	Applicant Explanation
						breast, 3 liver, and lymph node by spiral CT & NT=2 liver and breast by spiral CT. IRC observed PD 15NOV04 due to increase in target lesions and worsening of nontarget lymph nodes. INV observed PD 02SEP04 due to worsening of nontarget lesions; however subject continued on study until there was an increase of target lesions and worsening of nontarget lesions on 15NOV04.

Data source: Study EGF 100151 report.

INVID = investigator ID, Subject = Subject ID, RANDDT = randomization date, DATE = TTP date, TIMEO = TTP duration (days), Reason = TTP reason, PD = disease progression, ACT = actual chemotherapy, such as toxicity, patient withdrew consent...., TMTGR = treatment group, 1=capecitabine + lapatinib, 2 = capecitabine alone, PC = PD day after cut-off day.

* Site Audited

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

The applicant submitted a TTP analysis update using the Study 100151 termination date, April 3, 2006 as the cut off date. As shown in table below, 184 TTP events were identified by blind independent reviewers in 399 randomized subjects. The TTP analysis based on IRC was statistically significant in favor of combination arm with a hazard ratio of 0.57 (95% CI: 0.43, 0.77, two-sided p = 0.00013).

Table 92: Study EGF 100151 TTP analysis update based on IRC assessment (ITT, Apr 3, 2006 cut-off)

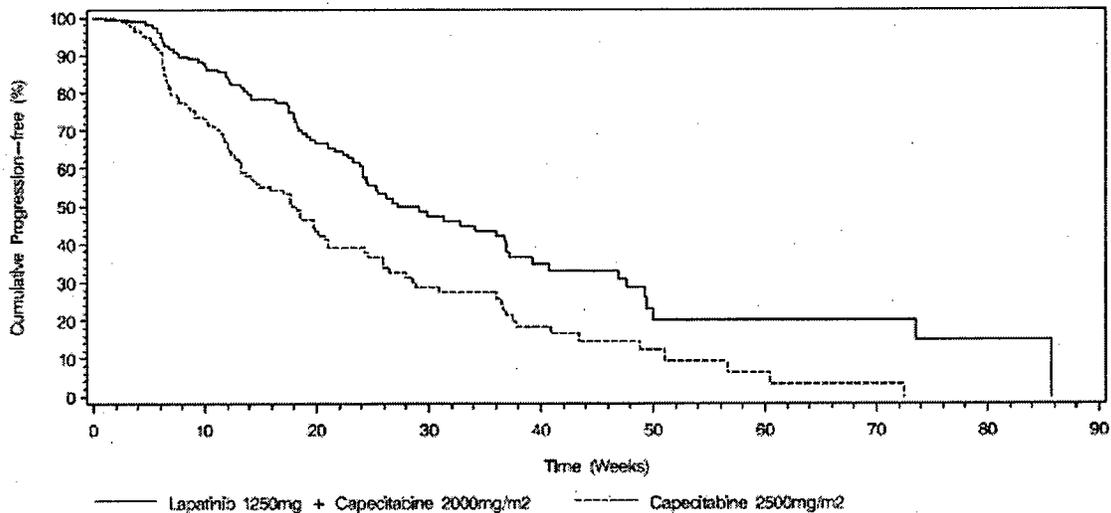
	Lapatinib + Capecitabine N=198	Capecitabine N=201	Difference in weeks
Progression and death, n (%)			
Progressed or died due to breast cancer	82 (41)	102 (51)	
Died due to cause other than breast cancer	0	5 (2)	
Censored, follow-up ended	20 (10)	23 (11)	
Censored, follow-up ongoing	96 (48)	71 (35)	
Cumulative incidence estimate of TTP, weeks			
1st Quartile	17.4	9.1	8.3
Median	27.1	18.6	8.5
3rd Quartile	49.4	36.9	12.5
Hazard ratio ¹ , [95% CI]	0.57 [0.43,0.77]		
Log-rank two-sided p-value ²	0.00013		

1. Hazard ratio of <1 indicates a lower risk with lapatinib + capecitabine compared to capecitabine.

2. Stratified two-sided log-rank test stratifying for stage of disease and site of disease at screening.

Data source: Study EGF 100151 report.

Table 93: Study EGF 100151 TTP update by IRC assessment - Kaplan Meier Estimates (ITT, Apr 3, 2006 cut-off)



1. Seven subjects who died due to causes other than breast cancer were censored in this analysis of the ITT Population.

Data source: Study EGF 100151 report.

According to the investigator analysis, the median TTP on the lapatinib + capecitabine combination arm was 23.9 weeks compared to 18.3 weeks on the capecitabine arm with a hazard ratio of 0.72 (95% CI: 0.56, 0.92, two-sided p = 0.00762, Table below).

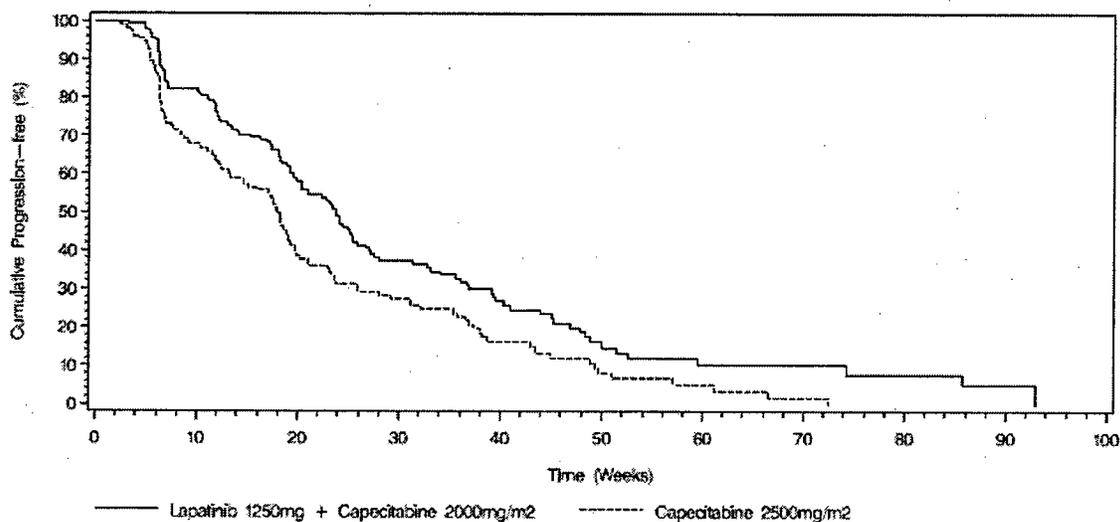
Table 94: Study EGF 100151 TTP analysis update based on investigator assessment (ITT, Apr 3, 2006 cut-off)

	Lapatinib + Capecitabine N=198	Capecitabine N=201
Progression and death, n (%)		
Progressed or died due to breast cancer	121 (61)	126 (63)
Died due to cause other than breast cancer	2 (1)	5 (2)
Censored, follow-up ended	9 (5)	14 (7)
Censored, follow-up ongoing	66 (33)	56 (28)
Cumulative estimate of TTP, weeks		
1st Quartile	12.0	6.9
Median	23.9	18.3
3rd Quartile	44.0	35.7
Hazard ratio ¹ , [95% CI]	0.72 [0.56,0.92]	
Log-rank two-sided p-value ²	0.00762	

Data source: Study EGF 100151 report.

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

Figure 12: Study EGF 100151 TTP update by investigator assessment - Kaplan Meier Estimates (ITT, Apr 3, 2006 cut-off)



1. Seven subjects who died due to causes other than breast cancer were censored in this analysis of the ITT Population.

Data source: Study EGF 100151 report.

Reviewer: The median TTP in the lapatinib + capecitabine group was 27.1 weeks compared to 18.6 weeks on the capecitabine group. This implies a 9 weeks improvement as compared to 17 weeks improvement at the earlier interim analysis (Nov 15 2005 cut-off). This reviewer verified the IRC TTP result.

The TTP analyses by IRC and investigator were consistent in TTP advantage found at the earlier interim analysis indicating there is a TTP improvement for the lapatinib combination arm. However, the magnitude of the improvement became smaller and the hazard ration became larger, which indicates differences in data availability for tumor assessment for independent review and investigator at the time of interim analysis and the clinical update.

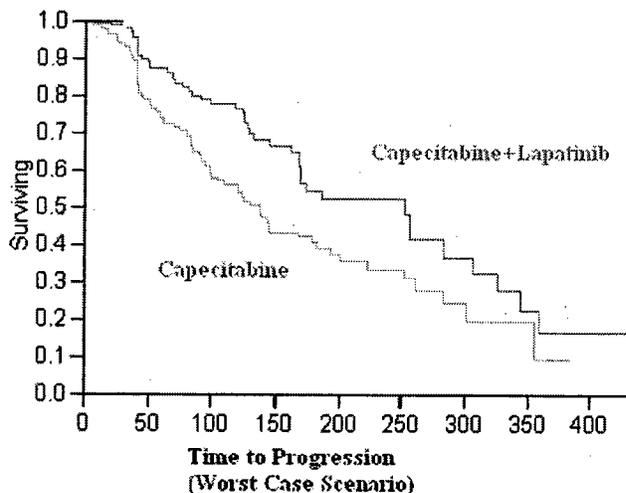
The analysis of difference in assessment of progression and response by IRC and investigator, the discussion of the TTP results difference by each assessment at each cut-off time were discussed in section 6.1.4.2.1.2.

10.1.1.3.2 Exploratory Analyses for TTP in ITT Population

10.1.1.3.2.1 Worst Case Scenario

An exploratory analysis for TTP was performed based on the worst-case scenario for lapatinib to evaluate if the discordance could affect the overall improvement on the lapatinib combination arm. The later event or censoring dates by the independent review committee assessment or investigator assessment, which ever comes later, were used if these were on the capecitabine arm. The earlier event or censoring date was chosen if it was on the lapatinib alone arm. Again, the lapatinib combination arm demonstrated an improved TTP. The medical team results are presented as below, and the statistical team verified results were presented in section 6.1.4.2.2.1.

Figure 13: FDA Kaplan-Meier Curve for TTP (Worst Case Scenario, ITT, Nov 15 2005 cut-off)



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Summary

Arm	N Failed	N Censored	Mean
Capecitabine/Lapatinib	47	116	221.1
Capecitabine	74	87	171.5
Combined	121	203	194.6

TTP in weeks (Worst Case Scenario)

Arm	Median Time	25% Failures	75% Failures
Capecitabine/Lapatinib	36.1	18	49.3
Capecitabine	19.6	8.6	40.7

Log Rank P value: 0.0051 (using JMP software)

10.1.1.3.2.2 Testing the frequency of event

As mentioned briefly in section 6.1.4.2.2.1, the statistical reviewer, Dr. Ko, conducted a revised TTP analyses of both cut-offs, interim analysis and clinical up date. The earlier date of TTP event and censoring by either independent review committee (IRC) assessment or investigator assessment, which ever comes first, were chosen for both arms, as shown below.

Table 95: FDA revised TTP analyses (Nov 15 2005 and Apr 3 2006 cut-offs)

	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	0.456 (0.297 – 0.702)		0.555 (0.404 – 0.764)	
p-value from stratified log-rank test	0.00027		0.00058	

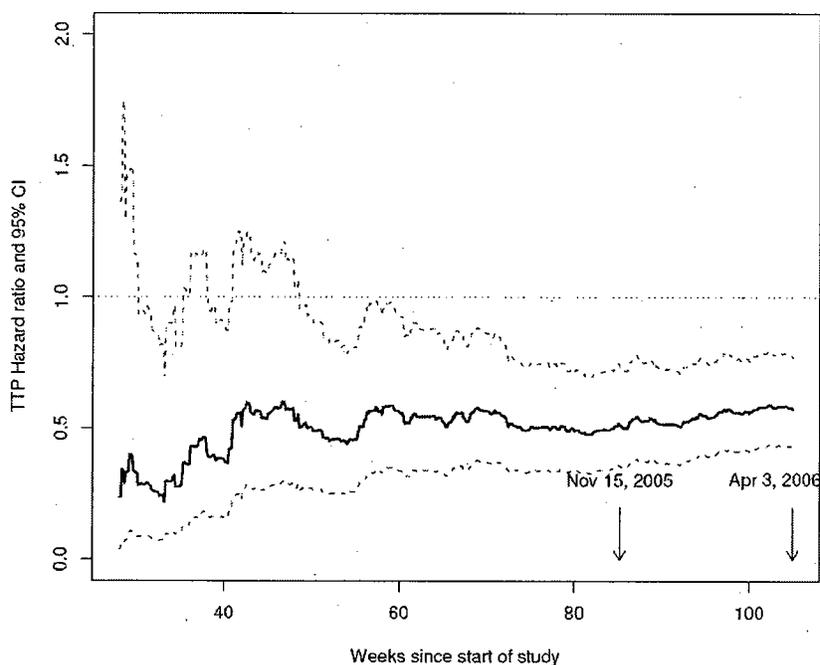
IND = Independent Reviewer Analysis, INV = Investigators Analysis, LC = Lapatinib + Capecitabine, C = Capecitabine, TA = tumor assessment, BL = baseline.

Source: Study EGF 100151 report.

Reviewer: Compare to the IRC assessed TTP analysis; there were 57 and 37 subjects data were changed following the rule above for interim analysis and update analysis, respectively. The revised TTP may be more précised than IRC TTP. One explanation is that events are better distributed near the median TTP in the revised TTP analyses. See below for details.

Although that the applicant has provided are hazard ratio (HR) stability analysis to support the consistency between the TTP interim analysis and TTP up date analysis. As shown in the figure below, the TTP HR appears to be stabilized before 80 weeks, which is before both cut-off dates.

Figure 14: Applicant Analysis on TTP HR Stability



Source: Study EGF 100151 report applicant analyses

However, the IRC event distribution analysis conducted by the FDA statistical reviewer, Dr. Ko, indicated that lack of events assessed near the median TTP of lapatinib combination arm at interim analysis but improved at the up date analysis, versus events were better distributed near the median TTP of the capecitabine control arm (see following figure). These suggest the possibility of insufficient or missing tumor assessments for the testing arm, especially at the time of interim analysis, which explains why there was a 9.6 weeks difference in median TTP for the lapatinib arm and only 0.4-week difference for that of capecitabine arm. When revised TTP analysis merging the events resulting the events to be better distributed near the median TTP, and therefore, providing a better TTP outcome for the testing arm (Table below).

Table 96: FDA revised TTP versus independent TTP (Apr 3 2006 cut-off)

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TTP Analyses	IRC (N = 399)		FDA Revised (N = 399)	
	L+C (N = 198)	C (N = 201)	L+C (N = 198)	C (N = 201)
# Events (%)	82 (41%)	102 (51%)	70	91
PD	69	86	65	82
BC death	13	16	5	9
Other death	0	5	0	5
Kaplan-Meier estimates of TTP (weeks)				
25% TTP	17.4 (13.6 – 19.9)	9.1 (6.7 – 11.7)	17.4 (13.6 – 19.4)	9.9 (6.9 – 12.3)
Median TTP	27.1 (24.1 – 36.9)	17.9 (13.7, 20.7)	32.9 (24.4 – 40.7)	18.6 (14.6 – 25.9)
75% TTP	49.4 (39.3 – 85.7)	36.4 (26.4 – 40.9)	85.7 (46.9 – 87.7)	36.9 (28.6 – 48.9)
Hazard Ratio	0.553 (0.412 – 0.743)		0.555 (0.404 – 0.764)	
p-value from stratified log-rank test	0.00012		0.00058	

IRC = independent assessment, L+C = lapatinib combination arm, C = capecitabine arm, PD = disease progression, BC = breast cancer.

Source: Provided by FDA statistical reviewer, Dr. Ko

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Table 97: FDA comparison of IRC and INV event distribution (Nov 15 2005 and Apr 3 2006 cut-off)

TMTGR	TTE (wk)	IRC		INV		IND TTE (wk)	IRC		INV	
		proportion event free at interim	proportion event free at update	progression free at interim	progression free at update		proportion event free at interim	proportion event free at update	progression free at interim	progression free at update
1	25.286	0.545	0.543	23.286	0.515	2	15.857	0.542	17.143	0.568
1	25.429	0.531	0.531	23.429	0.508	2	17.000	0.533	17.286	0.535
1	26.143	0.520	0.520	23.857	0.601	2	17.571	0.530	17.571	0.556
1	26.714	0.523	0.509	23.857	0.601	2	17.571	0.520	17.571	0.556
1	27.143	0.497	0.497	24.143	0.492	2	17.571	0.508	17.714	0.545
1	29.143	0.485	0.485	24.143	0.557	2	18.286	0.496	17.857	0.521
1	29.857	0.472	0.472	24.143	0.469	2	18.571	0.463	18.143	0.489
1	31.286	0.459	0.459	24.429	0.542	2	18.571	0.483	18.286	0.497
1	32.857	0.446	0.446	24.857	0.453	2	18.571	0.470	18.286	0.497
1	34.143	0.434	0.434	25.000	0.445	2	19.143	0.470	18.286	0.466
1	36.000	0.420	0.420	25.286	0.438	2	19.143	0.470	18.286	0.451
1	36.714	0.494	0.407	25.429	0.422	2	19.714	0.456	18.571	0.443
1	36.857	0.436	0.379	25.429	0.414	2	19.857	0.433	18.571	0.484
1	36.857	0.436	0.379	25.857	0.493	2	19.857	0.433	18.857	0.443
				26.714	0.406					

IRC = independent assessment, INV = investigator assessment, TMTGR = treatment group, 1 = lapatinib combination arm, 2 = capecitabine arm, TTE = time to event.
 Source: Provided by FDA statistical reviewer, Dr. Ko

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10.1.1.3.2.3 Tumor assessment

The analyses on the adequacy and frequency of tumor evaluation/assessment by the investigator and independent review committee is summarized in section 6.1.4.2.2.2.

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

The analysis to compare number of patients censored and the time intervals between the cut-off date and censoring date by both assessment party and both cut of dates were described in section 6.1.4.2.2.3.

To explore this concern in detail, clinical and statistical reviewer have selected 15 cases that IRC determined TTP events as death dated later than the investigator's TTP event of disease progression date, for detailed investigation. For each case, CRF and EGF 100151 study data sets were referenced, as shown in the following table.

To address this problem, the reviewer reviewed CFR of all cases that independent review TTP event dated later than that of the investigator, compared with the applicant provided data set and conducted the following exploratory analyses.

The result and conclusion of these analyses were described in section 6.1.4.2.2.3.

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Table 98: CRF and data set review of 15 cases

INVID	Sub ID	IRC vs. INV (days)	Difference in Days	Arm	INV Tumor Measurement by CRF	Note on CRF (INV assessment)	Dates of no scans for IRC review	IND TTP event & date	Off Study Tx**	
									11/15/05	4/3/06
054788	50	/	104	1	Single ML selected, one measurement for PR (69 to 49mm) on record	PR Oct 4 04 (12 wks), PD Jan 20 05 (24 wks), death study w/d was Feb 02 05 then change to death day.	01/20/05-	Death, same date	n/a	n/a
034749	122	/	37	1	3 MLs recored TM at 6 wks only	SD Jan 16 05 (24 wks), PD on May 22 05 by INV then change to SD (36 wks), death.	05/22/05-	Death, same date	n/a	n/a
005117	325	/	123	1	One ML recored, NM of LV and BS	PD Mar 21 05 (6 wks), Death	03/21/05-	Death, same date	n/a	n/a
001431	403	/	172	1	4 LV ML recorded for PR on Feb 22 05	PR Jan 24 05 (6 wks), PD May 26 05 (24 wks), death	05/26/05-	Death, same date	No	No
041380	551	/	154	1	5 ML followed	PD Jul 21 05 (1 yr), death	07/21/05-	C on Nov 15 05 cut-off, Death, same date or <u>on cut-off</u>	No	No
058148	*799	/	127	1	Baseline sc Oct 28 04, 1 st TM Jan 3 05	PD Jan 3 05 (6 wk), Death on	01/05/05-	Death, same date	n/a	n/a
033588	*1300	/	35	1	Single ML Jun 8 05 vs. Aug 5 05	PD Dec 8 05 (24 wks), death	IRC reviewed scan 7/28/05 and 10/18/05. no scan time should be	Death, same date	n/a	n/a

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INVID	Sub ID	IRC vs. INV (days)	Difference in Days	Arm	INV Tumor Measurement by CRF	Note on CRF (INV assessment)	Dates of no scans for IRC review	IND TTP event & date	Off Study Tx**	
									11/15/05	4/3/06
006342	1312	✓	141	1	3 MLs	PD Sep 9 05	10/18/05 to		n/a	No
040179	413		65	2	2 MLs	PD Jan 14 05 Death	09/14/05-	Death, same date	n/a	n/a
030076	451		33	2	4 ML 10/5/05 & 12/1/05	PD Dec 1 05 (6 eks), Death	No scans except baseline	Death =	n/a	n/a
034246	618		27	2	4 BL MLs Jul 21 04	Sx PD Aug 31 04 (8 wk), death	8/31/04-	Death, same date	n/a	n/a
058191	695		84	2	3 ML	PD May 16 05 (6 eks), Death	05/16/05-	Death, same date	No	No
027231	710*		20	2	6 ML Jul 19 05 & Sep 06 05, no obj PD.	Sx PD Sep 6 (4 wk), Death	9/6/05-	Death, same date	No	No
057790	795		138	2	4 ML	PR Dec 21 04 (6 wk), PD Jul 5 05?, death	7/26/05-	C for Nov 15 05, Death for	No	No
061546	1033*	✓	90	2	4 ML TM on Oct 24 05 no Obj PD	Sx PD Nov 25 05?, death	10/24/05-	C for Nov 15 05, Death for	n/a	n/a

ML = measurable lesion, LV = liver lesion, NE = no evaluation, PD = progression of disease, BL = baseline, TM = tumor measurement, Obj = objective.

* scans to check in IRC files and to be pulled for date verification.

** Based on applicants Status.JMP data set, there were 118/324 and 198/399 subjects recordeed for post study treatment at Nov 15 2005 and Apr 3 2006 cut-off dates, respectively.

C- censor, Treatment arm: 1 = lapatinib + capecitabine, 2 = capecitabine

10.1.1.4 Safety

The detailed safety review is described in Section 7. The safety population treatment status at Nov 15 2005 cut-off are as below.

Table 99: Study EGF100151 subject treatment status (SP, Nov 15 2005 cut-off)

Treatment		Lapatinib + Capecitabine N=164 (%)	Capecitabine N=152 (%)	Total N=316 (%)
Status	Terminated Permanently	129 (79)	131 (86)	260 (82)
	Ongoing ¹	35 (21)	21 (14)	56 (18)
Primary Reason for treatment termination	Progressive disease	95 (74)	103 (79)	198 (76)
	Adverse event	22 (17)	16 (12)	38 (15)
	Consent withdrawn	6 (5)	3 (2)	9 (3)
	Other	5 (4) ²	4 (3) ³	9 (3)
	Death	0	3 (2)	3 (1)
	Protocol violation	1 (<1)	1 (<1)	2 (<1)
	Discontinuation by study sponsor	0	1 (<1)	1 (<1)

Data Source: Study EGF100151 study report.

1. As of clinical cut-off date of 15 November 2005.
2. Two subjects had study medication discontinued due to a lack of clinical benefit, one subject due to receiving glucocorticoid therapy, one subject due to positive histology and one subject had study medication discontinued at the investigator's discretion.
3. Three subjects had study medication discontinued at the investigator's discretion, and one subject due to the study sponsor withdrawing the medication because of a dosing error.

Reviewer: Two subjects (investigator/subject ID 043965/487 and 060439/1361) of lapatinib/capecitabine group, had study medication discontinued due to a lack of clinical benefit, one subject due to receiving glucocorticoid therapy, one subject due to positive histology and one subject had study medication discontinued at the investigator's discretion.

Three subjects (Investigator/subject ID 044034/57, 057790/796 and 015295/203) of capecitabine group had study medication discontinued at the investigator's discretion, and one subject (Investigator/subject ID 033602/480) of capecitabine group, due to the study sponsor withdrawing the medication as a result of a dosing error.

All AEs and SAEs recorded in study EGF 100151 regardless relationship are summarized by body system in the table below.

Table 100: Study EGF 100151 all AEs and SAEs regardless of relationship (SP, Nov 15 2005 cut-off)

MedDRA Preferred Terms	Lapatinib + capecitabine AEs N = 164				Capecitabine AEs N = 152			
	All	%	G3-4	%	All	%	G3-4	%
Blood and lymphatic system disorders								
Anemia	9	5	0	0	7	5	1	1
Leukopenia	5	3	0	0	2	1	1	1

MedDRA Preferred Terms	Lapatinib + capecitabine AEs N = 164				Capecitabine AEs N = 152			
	All	%	G3-4	%	All	%	G3-4	%
Neutropenia	4	2	3	2	9	6	4	3
Thrombocytopenia	4	2	1	1	2	1	2	1
Granulocytopenia	1	1	0	0	0	0	0	0
Haematotoxicity	1	1	0	0	0	0	0	0
Lymphopenia	1	1	0	0	1	1	0	0
Lymph node pain	0	0	0	0	1	1	0	0
Cardiac disorders								
Tachycardia	2	1	0	0	0	0	0	0
Arrhythmia	1	1	0	0	1	1	0	0
Palpitations	1	1	0	0	2	1	0	0
Pericarditis	1	1	0	0	0	0	0	0
Prinzmetal angina	1	1	0	0	0	0	0	0
Supraventricular extrasystoles	1	1	0	0	0	0	0	0
Ventricular dysfunction	1	1	0	0	1	1	0	0
Cardiac failure	0	0	0	0	1	1	0	0
Sinus tachycardia	0	0	0	0	1	1	0	0
Supraventricular tachycardia	0	0	0	0	1	1	1	1
Ear and labyrinth disorders								
Ear pain	2	1	0	0	1	1	0	0
Vertigo	2	1	0	0	4	3	0	0
Eye disorders								
Lacrimation increased	6	4	0	0	5	3	0	0
Conjunctivitis	5	3	0	0	1	1	0	0
Dry eye	5	3	0	0	2	1	0	0
Eye irritation	4	2	0	0	1	1	0	0
Visual disturbance	3	2	0	0	4	3	0	0
Eye pruritus	2	1	0	0	0	0	0	0
Ocular icterus	2	1	0	0	0	0	0	0
Vision blurred	2	1	0	0	2	1	0	0
Abnormal sensation in eye	1	1	0	0	0	0	0	0
Diplopia	1	1	1	1	2	1	0	0
Eyelid edema	1	1	0	0	0	0	0	0
Eyelid pain	1	1	0	0	0	0	0	0
Photophobia	1	1	0	0	0	0	0	0
Xerophthalmia	1	1	0	0	0	0	0	0
Erythema of eyelid	0	0	0	0	1	1	0	0
Eye discharge	0	0	0	0	1	1	0	0
Eye pain	0	0	0	0	3	2	0	0
Eyelid margin crusting	0	0	0	0	1	1	0	0
Keratoconjunctivitis sicca	0	0	0	0	1	1	0	0
Orbital edema	0	0	0	0	1	1	0	0
Photopsia	0	0	0	0	1	1	0	0
Vitreous floaters	0	0	0	0	1	1	0	0
Gastrointestinal disorders								
Diarrhea	98	60	21	13	60	39	17	11
Nausea	72	44	3	2	63	41	3	2
Vomiting	43	26	3	2	36	24	3	2
Stomatitis	24	15	0	0	18	12	1	1
Dyspepsia	18	11	0	0	5	3	0	0
Abdominal pain	16	10	2	1	25	16	2	1
Constipation	16	10	0	0	17	11	1	1
Abdominal pain upper	12	7	0	0	8	5	0	0
Mouth ulceration	7	4	0	0	4	3	0	0
Dry mouth	6	4	0	0	4	3	1	1
Flatulence	5	3	0	0	2	1	0	0

MedDRA Preferred Terms	Lapatinib + capecitabine AEs N = 164				Capecitabine AEs N = 152			
	All	%	G3-4	%	All	%	G3-4	%
Hemorrhoids	5	3	0	0	1	1	0	0
Dysphagia	4	2	0	0	2	1	0	0
Abdominal distension	3	2	0	0	4	3	1	1
Cheilitis	3	2	0	0	0	0	0	0
Gastroesophageal reflux disease	3	2	1	1	1	1	0	0
Lip blister	3	2	0	0	1	1	0	0
Lip dry	3	2	0	0	1	1	0	0
Lip ulceration	3	2	0	0	1	1	0	0
Gingival pain	2	1	0	0	1	1	0	0
Glossodynia	2	1	0	0	0	0	0	0
Haematochezia	2	1	0	0	0	0	0	0
Abdominal discomfort	1	1	0	0	0	0	0	0
Anal fissure	1	1	0	0	0	0	0	0
Aphthous stomatitis	1	1	0	0	0	0	0	0
Chapped lips	1	1	0	0	1	1	0	0
Colitis	1	1	0	0	0	0	0	0
Epigastric discomfort	1	1	0	0	0	0	0	0
Gastritis	1	1	0	0	2	1	0	0
Gastrointestinal hemorrhage	1	1	0	0	0	0	0	0
Gastrointestinal pain	1	1	0	0	0	0	0	0
Gingivitis	1	1	0	0	2	1	0	0
Hiatus hernia	1	1	0	0	0	0	0	0
Mouth cyst	1	1	0	0	0	0	0	0
Oral mucosal exfoliation	1	1	0	0	0	0	0	0
Rectal hemorrhage	1	1	0	0	0	0	0	0
Retching	1	1	0	0	0	0	0	0
Abdominal pain lower	0	0	0	0	3	2	0	0
Colonic obstruction	0	0	0	0	1	1	1	1
Duodenal ulcer perforation	0	0	0	0	1	1	1	1
Eructation	0	0	0	0	1	1	0	0
Feces pale	0	0	0	0	1	1	0	0
Gastric disorder	0	0	0	0	1	1	0	0
Gastric ulcer	0	0	0	0	1	1	1	1
Hematemesis	0	0	0	0	1	1	0	0
Esophageal pain	0	0	0	0	1	1	0	0
Oral pain	0	0	0	0	1	1	0	0
Small intestinal obstruction	0	0	0	0	1	1	1	1
Swollen tongue	0	0	0	0	1	1	0	0
Toothache	0	0	0	0	1	1	0	0
General disorders and administration site conditions								
Fatigue	29	18	3	2	41	27	6	4
Mucosal inflammation	18	11	0	0	19	13	3	2
Edema peripheral	11	7	1	1	5	3	1	1
Asthenia	10	6	0	0	18	12	3	2
Chest pain	8	5	1	1	4	3	1	1
Pyrexia	8	5	0	0	12	8	0	0
Pain	5	3	1	1	3	2	1	1
Chills	3	2	0	0	4	3	0	0
Face edema	2	1	0	0	1	1	0	0
Impaired healing	2	1	0	0	0	0	0	0
Abasia	1	1	0	0	1	1	1	1
Axillary pain	1	1	0	0	3	2	0	0
Gait disturbance	1	1	0	0	1	1	1	1
Inflammation	1	1	0	0	1	1	0	0
Necrosis	1	1	0	0	0	0	0	0

Clinical Review
 Qin Ryan, MD, PhD
 NDA 22059-000
 Tykerb (lapatinib)

MedDRA Preferred Terms	Lapatinib + capecitabine AEs N = 164				Capecitabine AEs N = 152			
	All	%	G3-4	%	All	%	G3-4	%
Edema	1	1	0	0	1	1	0	0
Influenza like illness	0	0	0	0	3	2	0	0
Irritability	0	0	0	0	1	1	0	0
Localized edema	0	0	0	0	2	1	0	0
Hepatobiliary disorders								
Hyperbilirubinemia	5	3	1	1	3	2	1	1
Hepatic function abnormal	2	1	1	1	0	0	0	0
Budd-Chiari syndrome	1	1	0	0	0	0	0	0
Cholecystitis	1	1	0	0	0	0	0	0
Hepatic pain	1	1	0	0	0	0	0	0
Hepatotoxicity	1	1	0	0	1	1	0	0
Jaundice	1	1	0	0	0	0	0	0
Hepatitis	0	0	0	0	1	1	0	0
Immune system disorders								
Hypersensitivity	1	1	0	0	0	0	0	0
Multiple allergies	0	0	0	0	1	1	0	0
Seasonal allergy	0	0	0	0	1	1	0	0
Infections and infestations								
Nasopharyngitis	7	4	0	0	10	7	0	0
Localized infection	6	4	0	0	2	1	0	0
Nail infection	6	4	1	1	3	2	0	0
Urinary tract infection	4	2	1	1	4	3	0	0
Oral candidiasis	3	2	0	0	0	0	0	0
Sinusitis	3	2	0	0	2	1	0	0
Upper respiratory tract infection	3	2	0	0	4	3	2	1
Bronchitis	2	1	0	0	2	1	0	0
Erysipelas	2	1	1	1	0	0	0	0
Infection	2	1	0	0	2	1	0	0
Influenza	2	1	1	1	1	1	0	0
Lower respiratory tract infection	2	1	0	0	1	1	0	0
Paronychia	2	1	0	0	1	1	0	0
Rhinitis	2	1	0	0	1	1	0	0
Skin infection	2	1	0	0	3	2	0	0
Tooth abscess	2	1	0	0	1	1	0	0
Viral infection	2	1	0	0	1	1	0	0
Catheter related infection	1	1	1	1	0	0	0	0
Cellulitis	1	1	1	1	0	0	0	0
Ear infection	1	1	0	0	0	0	0	0
Escherichia sepsis	1	1	1	1	0	0	0	0
Fungal rash	1	1	0	0	0	0	0	0
Fungal skin infection	1	1	0	0	0	0	0	0
Gastroenteritis	1	1	0	0	0	0	0	0
Genital infection fungal	1	1	0	0	0	0	0	0
Gingival abscess	1	1	0	0	0	0	0	0
Herpes simplex	1	1	0	0	3	2	0	0
Herpes zoster	1	1	0	0	0	0	0	0
Hordeolum	1	1	0	0	0	0	0	0
Lymphangitis	1	1	0	0	1	1	0	0
Pyelonephritis	1	1	0	0	0	0	0	0
Sialoadenitis	1	1	0	0	0	0	0	0
Breast infection	0	0	0	0	1	1	0	0
Conjunctivitis infective	0	0	0	0	1	1	0	0
Cystitis	0	0	0	0	2	1	0	0
Diarrhea infectious	0	0	0	0	1	1	1	1
Eye infection	0	0	0	0	2	1	0	0

MedDRA Preferred Terms	Lapatinib + capecitabine AEs N = 164				Capecitabine AEs N = 152			
	All	%	G3-4	%	All	%	G3-4	%
Hand-foot-and-mouth disease	0	0	0	0	1	1	0	0
Herpes virus infection	0	0	0	0	1	1	0	0
Mastitis	0	0	0	0	1	1	0	0
Nail bed infection	0	0	0	0	1	1	0	0
Onychomycosis	0	0	0	0	1	1	0	0
Tinea pedis	0	0	0	0	1	1	0	0
Tooth infection	0	0	0	0	1	1	0	0
Vaginal candidiasis	0	0	0	0	1	1	0	0
Vulvovaginal mycotic infection	0	0	0	0	1	1	0	0
Injury, poisoning and procedural complications								
Skin laceration	2	1	0	0	0	0	0	0
Back injury	1	1	1	1	0	0	0	0
Medical device complication	1	1	0	0	0	0	0	0
Rib fracture	1	1	0	0	0	0	0	0
Thermal burn	1	1	0	0	1	1	0	0
Wound	1	1	0	0	1	1	0	0
Contusion	0	0	0	0	2	1	0	0
Excoriation	0	0	0	0	1	1	0	0
Fibula fracture	0	0	0	0	1	1	0	0
Radiation injury	0	0	0	0	1	1	0	0
Radiation skin injury	0	0	0	0	1	1	0	0
Tibia fracture	0	0	0	0	1	1	1	1
Upper limb fracture	0	0	0	0	1	1	1	1
Wrist fracture	0	0	0	0	1	1	1	1
Investigations								
Blood bilirubin increased	7	4	1	1	1	1	0	0
Ejection fraction decreased	6	4	1	1	0	0	0	0
Alanine aminotransferase increased	4	2	0	0	2	1	0	0
Aspartate aminotransferase increased	4	2	1	1	3	2	0	0
Blood alkaline phosphatase increased	4	2	0	0	2	1	0	0
Haemoglobin decreased	4	2	0	0	2	1	0	0
Weight decreased	4	2	0	0	8	5	0	0
Blood albumin decreased	1	1	0	0	0	0	0	0
Blood bicarbonate decreased	1	1	0	0	0	0	0	0
Blood creatine increased	1	1	0	0	0	0	0	0
Blood phosphorus decreased	1	1	0	0	0	0	0	0
Cardiac murmur	1	1	0	0	0	0	0	0
Creatinine renal clearance decreased	1	1	0	0	0	0	0	0
International normalised ratio increased	1	1	1	1	0	0	0	0
Platelet count decreased	1	1	0	0	0	0	0	0
Respiratory rate increased	1	1	0	0	0	0	0	0
White blood cell count decreased	1	1	0	0	2	1	1	1
Blood alkaline phosphatase decreased	0	0	0	0	1	1	0	0
Blood calcium increased	0	0	0	0	1	1	0	0
Blood chloride decreased	0	0	0	0	2	1	0	0
Blood creatinine decreased	0	0	0	0	1	1	1	1
Blood creatinine increased	0	0	0	0	1	1	0	0
Blood urea increased	0	0	0	0	1	1	0	0
Blood urea nitrogen/creatinine ratio increased	0	0	0	0	1	1	0	0
Carcinoembryonic antigen increased	0	0	0	0	1	1	0	0
Haemoglobin	0	0	0	0	1	1	0	0
Hemoglobin increased	0	0	0	0	1	1	0	0
Hepatic enzyme increased	0	0	0	0	1	1	1	1
Neutrophil count	0	0	0	0	2	1	1	1
Neutrophil count decreased	0	0	0	0	2	1	0	0

MedDRA Preferred Terms	Lapatinib + capecitabine AEs N = 164				Capecitabine AEs N = 152			
	All	%	G3-4	%	All	%	G3-4	%
Neutrophil count increased	0	0	0	0	1	1	1	1
Platelet count increased	0	0	0	0	1	1	0	0
Prothrombin time prolonged	0	0	0	0	1	1	0	0
Red blood cell count decreased	0	0	0	0	1	1	0	0
Weight increased	0	0	0	0	1	1	0	0
Metabolism and nutrition disorders								
Anorexia	25	15	1	1	30	20	1	1
Dehydration	7	4	3	2	7	5	2	1
Hypokalaemia	6	4	5	3	5	3	2	1
Decreased appetite	5	3	0	0	4	3	0	0
Acidosis	1	1	1	1	0	0	0	0
Hypercholesterolaemia	1	1	0	0	0	0	0	0
Hyperglycemia	1	1	0	0	4	3	0	0
Hyperuricaemia	1	1	0	0	0	0	0	0
Hypoalbuminaemia	1	1	0	0	2	1	0	0
Hypocalcaemia	1	1	0	0	1	1	0	0
Hypochloraemia	1	1	0	0	0	0	0	0
Hyponatraemia	1	1	1	1	2	1	1	1
Hypoproteinaemia	1	1	0	0	0	0	0	0
Lactose intolerance	1	1	0	0	0	0	0	0
Diabetes mellitus	0	0	0	0	1	1	0	0
Hypercalcaemia	0	0	0	0	1	1	1	1
Hypovolaemia	0	0	0	0	1	1	1	1
Musculoskeletal and connective tissue disorders								
Pain in extremity	20	12	1	1	12	8	1	1
Back pain	17	10	2	1	9	6	1	1
Arthralgia	12	7	1	1	6	4	0	0
Bone pain	11	7	2	1	6	4	1	1
Muscle spasms	7	4	0	0	2	1	0	0
Myalgia	6	4	1	1	6	4	0	0
Musculoskeletal chest pain	3	2	0	0	5	3	0	0
Buttock pain	2	1	0	0	0	0	0	0
Neck pain	2	1	0	0	2	1	0	0
Arthritis	1	1	1	1	1	1	0	0
Joint stiffness	1	1	0	0	0	0	0	0
Muscular weakness	1	1	0	0	2	1	1	1
Musculoskeletal discomfort	1	1	0	0	0	0	0	0
Musculoskeletal stiffness	1	1	0	0	0	0	0	0
Osteonecrosis	1	1	1	1	0	0	0	0
Pain in jaw	1	1	0	0	1	1	0	0
Sensation of heaviness	1	1	0	0	0	0	0	0
Shoulder pain	1	1	0	0	3	2	0	0
Flank pain	0	0	0	0	1	1	0	0
Musculoskeletal pain	0	0	0	0	1	1	1	1
Sacral pain	0	0	0	0	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)								
Acute myeloid leukaemia	1	1	1	1	0	0	0	0
Cancer pain	1	1	1	1	0	0	0	0
Malignant melanoma	1	1	1	1	0	0	0	0
Metastases to central nervous system	1	1	0	0	0	0	0	0
Metastatic pain	1	1	1	1	0	0	0	0
Neoplasm skin	1	1	0	0	0	0	0	0
Malignant pleural effusion	0	0	0	0	1	1	1	1
Nervous system disorders								
Headache	15	9	0	0	19	13	2	1

MedDRA Preferred Terms	Lapatinib + capecitabine AEs N = 164				Capecitabine AEs N = 152			
	All	%	G3-4	%	All	%	G3-4	%
Dysgeusia	8	5	0	0	3	2	0	0
Lethargy	8	5	2	1	4	3	0	0
Dizziness	7	4	0	0	13	9	2	1
Paraesthesia	5	3	0	0	8	5	0	0
Hypoaesthesia	3	2	0	0	1	1	0	0
Neuropathy peripheral	3	2	0	0	5	3	0	0
Hyperaesthesia	2	1	0	0	1	1	0	0
Neuropathy	2	1	0	0	2	1	0	0
Peripheral sensory neuropathy	2	1	0	0	8	5	0	0
Balance disorder	1	1	0	0	1	1	0	0
Coordination abnormal	1	1	0	0	1	1	1	1
Dizziness postural	1	1	0	0	0	0	0	0
Dysaesthesia	1	1	0	0	1	1	0	0
3rd nerve paralysis	1	1	0	0	0	0	0	0
Neuralgia	1	1	1	1	1	1	0	0
Parosmia	1	1	0	0	0	0	0	0
Sensory disturbance	1	1	0	0	0	0	0	0
Somnolence	1	1	0	0	0	0	0	0
Spinal cord compression	1	1	1	1	0	0	0	0
Syncope	1	1	1	1	1	1	1	1
Cerebellar syndrome	0	0	0	0	1	1	0	0
Cognitive disorder	0	0	0	0	1	1	0	0
Convulsion	0	0	0	0	1	1	0	0
Dysarthria	0	0	0	0	2	1	0	0
Facial neuralgia	0	0	0	0	1	1	0	0
Facial palsy	0	0	0	0	1	1	0	0
Hypokinesia	0	0	0	0	1	1	0	0
Memory impairment	0	0	0	0	1	1	0	0
Migraine	0	0	0	0	2	1	0	0
Neurotoxicity	0	0	0	0	4	3	1	1
Peripheral motor neuropathy	0	0	0	0	2	1	0	0
Sinus headache	0	0	0	0	1	1	0	0
Speech disorder	0	0	0	0	1	1	0	0
Psychiatric disorders								
Insomnia	16	10	1	1	9	6	0	0
Anxiety	7	4	1	1	3	2	0	0
Depression	4	2	2	1	4	3	0	0
Depressed mood	2	1	0	0	0	0	0	0
Attention deficit/hyperactivity disorder	1	1	0	0	0	0	0	0
Confusional state	1	1	0	0	0	0	0	0
Emotional disorder	1	1	0	0	0	0	0	0
Tearfulness	1	1	0	0	0	0	0	0
Restlessness	0	0	0	0	1	1	0	0
Renal and urinary disorders								
Dysuria	4	2	1	1	1	1	0	0
Nephrolithiasis	2	1	0	0	0	0	0	0
Pollakiuria	2	1	0	0	1	1	0	0
Bladder pain	1	1	0	0	0	0	0	0
Hydronephrosis	1	1	0	0	0	0	0	0
Choluria	0	0	0	0	1	1	0	0
Renal pain	0	0	0	0	1	1	0	0
Reproductive system and breast disorders								
Breast pain	3	2	0	0	2	1	1	1
Vaginal hemorrhage	3	2	0	0	0	0	0	0
Genital pain female	1	1	0	0	0	0	0	0

MedDRA Preferred Terms	Lapatinib + capecitabine AEs N = 164				Capecitabine AEs N = 152			
	All	%	G3-4	%	All	%	G3-4	%
Genital pruritus female	1	1	0	0	1	1	0	0
Genital tract inflammation	1	1	0	0	0	0	0	0
Pelvic pain	1	1	0	0	1	1	0	0
Vaginal discharge	1	1	0	0	3	2	0	0
Metrorrhagia	0	0	0	0	2	1	0	0
Vaginal ulceration	0	0	0	0	1	1	0	0
Respiratory, thoracic and mediastinal disorders								
Dyspnoea	18	11	5	3	10	7	3	2
Cough	11	7	0	0	13	9	0	0
Epistaxis	11	7	0	0	4	3	0	0
Pharyngolaryngeal pain	3	2	0	0	2	1	0	0
Rhinorrhoea	3	2	0	0	1	1	0	0
Asthma	2	1	1	1	0	0	0	0
Nasal ulcer	2	1	0	0	0	0	0	0
Pulmonary embolism	2	1	2	1	1	1	1	1
Bronchospasm	1	1	1	1	0	0	0	0
Dry throat	1	1	0	0	0	0	0	0
Dyspnoea exacerbated	1	1	0	0	0	0	0	0
Dyspnoea exertional	1	1	1	1	0	0	0	0
Hemoptysis	1	1	1	1	1	1	0	0
Nasal congestion	1	1	0	0	3	2	0	0
Nasal dryness	1	1	0	0	0	0	0	0
Pleural effusion	1	1	1	1	1	1	1	1
Productive cough	1	1	0	0	0	0	0	0
Rhinalgia	1	1	0	0	1	1	0	0
Rhinitis allergic	1	1	0	0	1	1	0	0
Dysphonia	0	0	0	0	1	1	0	0
Increased upper airway secretion	0	0	0	0	1	1	0	0
Pharyngeal inflammation	0	0	0	0	1	1	0	0
Pulmonary congestion	0	0	0	0	1	1	0	0
Respiratory tract congestion	0	0	0	0	1	1	0	0
Sinus congestion	0	0	0	0	1	1	0	0
Stridor	0	0	0	0	1	1	0	0
Upper respiratory tract congestion	0	0	0	0	1	1	0	0
Wheezing	0	0	0	0	1	1	0	0
Skin and subcutaneous tissue disorders								
Palmar-plantar erythrodysesthesia syndrome	80	49	12	7	74	49	16	11
Rash	45	27	2	1	23	15	2	1
Dry skin	18	11	0	0	8	5	0	0
Dermatitis acneiform	7	4	1	1	0	0	0	0
Nail disorder	7	4	0	0	2	1	0	0
Pruritus	7	4	0	0	4	3	0	0
Alopecia	6	4	0	0	4	3	0	0
Skin hyperpigmentation	5	3	0	0	6	4	0	0
Onycholysis	3	2	0	0	1	1	0	0
Skin lesion	3	2	0	0	0	0	0	0
Blister	2	1	1	1	2	1	0	0
Hyperhidrosis	2	1	0	0	1	1	0	0
Ingrowing nail	2	1	0	0	1	1	0	0
Pain of skin	2	1	0	0	1	1	0	0
Palmar erythema	2	1	0	0	0	0	0	0
Rash macular	2	1	0	0	0	0	0	0
Skin chapped	2	1	0	0	2	1	0	0
Skin discolouration	2	1	0	0	1	1	0	0
Skin ulcer	2	1	1	1	1	1	0	0

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MedDRA Preferred Terms	Lapatinib + capecitabine AEs N = 164				Capecitabine AEs N = 152			
	All	%	G3-4	%	All	%	G3-4	%
Erythema multiforme	1	1	0	0	0	0	0	0
Exfoliative rash	1	1	0	0	2	1	1	1
Hair growth abnormal	1	1	0	0	0	0	0	0
Heat rash	1	1	0	0	0	0	0	0
Nail discolouration	1	1	0	0	0	0	0	0
Nail dystrophy	1	1	0	0	0	0	0	0
Nail toxicity	1	1	0	0	0	0	0	0
Onychoclasia	1	1	0	0	0	0	0	0
Rash erythematous	1	1	0	0	0	0	0	0
Rash pruritic	1	1	0	0	2	1	0	0
Skin disorder	1	1	0	0	0	0	0	0
Skin exfoliation	1	1	0	0	2	1	0	0
Skin fissures	1	1	1	1	0	0	0	0
Skin hypertrophy	1	1	0	0	0	0	0	0
Xeroderma	1	1	0	0	0	0	0	0
Dermatitis exfoliative	0	0	0	0	1	1	0	0
Hypoaesthesia facial	0	0	0	0	1	1	0	0
Pigmentation disorder	0	0	0	0	2	1	0	0
Rash generalised	0	0	0	0	1	1	0	0
Surgical and medical procedures								
Incisional drainage	0	0	0	0	1	1	0	0
Vascular disorders								
Hot flush	2	1	0	0	2	1	0	0
Lymphoedema	2	1	1	1	1	1	0	0
Hypotension	1	1	0	0	2	1	0	0
Vasodilatation	1	1	0	0	0	0	0	0
Deep vein thrombosis	0	0	0	0	1	1	1	1
Diastolic hypertension	0	0	0	0	1	1	0	0
Flushing	0	0	0	0	1	1	0	0
Hypertension	0	0	0	0	1	1	0	0
Superior vena caval occlusion	0	0	0	0	1	1	1	1
Thrombophlebitis	0	0	0	0	1	1	0	0
Thrombosis	0	0	0	0	2	1	1	1
Vena cava thrombosis	0	0	0	0	1	1	1	1
Venous thrombosis	0	0	0	0	1	1	1	1

Source: Study EGF100151 original protocol.

The adverse events that less than 5% observed in study 100151, lapatinib and capecitabine combination arm as of interim analysis are summarized as below. The summary of less common adverse events at the time of clinical update were described in the section 7.1.6.

Table 101: Study EGF 100151 less common (<5%) AEs and SAEs regardless of relationship (SP, Nov 15 2005 cut-off)

MedDRA Preferred Terms	Lapatinib + capecitabine AEs N = 164				Capecitabine AEs N = 152			
	All	%	G3-4	%	All	%	G3-4	%
Blood and lymphatic system disorders								
Leukopenia	5	3	0	0	2	1	1	1
Neutropenia	4	2	3	2	9	6	4	3
Thrombocytopenia	4	2	1	1	2	1	2	1
Granulocytopenia	1	1	0	0	0	0	0	0
Haematotoxicity	1	1	0	0	0	0	0	0

MedDRA Preferred Terms	Lapatinib + capecitabine AEs N = 164				Capecitabine AEs N = 152			
	All	%	G3-4	%	All	%	G3-4	%
Lymphopenia	1	1	0	0	1	1	0	0
Cardiac disorders								
Tachycardia	2	1	0	0	0	0	0	0
Arrhythmia	1	1	0	0	1	1	0	0
Palpitations	1	1	0	0	2	1	0	0
Pericarditis	1	1	0	0	0	0	0	0
Prinzmetal angina	1	1	0	0	0	0	0	0
Supraventricular extrasystoles	1	1	0	0	0	0	0	0
Ventricular dysfunction	1	1	0	0	1	1	0	0
Ear and labyrinth disorders								
Ear pain	2	1	0	0	1	1	0	0
Vertigo	2	1	0	0	4	3	0	0
Eye disorders								
Lacrimation increased	6	4	0	0	5	3	0	0
Conjunctivitis	5	3	0	0	1	1	0	0
Dry eye	5	3	0	0	2	1	0	0
Eye irritation	4	2	0	0	1	1	0	0
Visual disturbance	3	2	0	0	4	3	0	0
Eye pruritus	2	1	0	0	0	0	0	0
Ocular icterus	2	1	0	0	0	0	0	0
Vision blurred	2	1	0	0	2	1	0	0
Abnormal sensation in eye	1	1	0	0	0	0	0	0
Diplopia	1	1	1	1	2	1	0	0
Eyelid edema	1	1	0	0	0	0	0	0
Eyelid pain	1	1	0	0	0	0	0	0
Photophobia	1	1	0	0	0	0	0	0
Xerophthalmia	1	1	0	0	0	0	0	0
Gastrointestinal disorders								
Mouth ulceration	7	4	0	0	4	3	0	0
Dry mouth	6	4	0	0	4	3	1	1
Flatulence	5	3	0	0	2	1	0	0
Hemorrhoids	5	3	0	0	1	1	0	0
Dysphagia	4	2	0	0	2	1	0	0
Abdominal distension	3	2	0	0	4	3	1	1
Cheilitis	3	2	0	0	0	0	0	0
Gastroesophageal reflux disease	3	2	1	1	1	1	0	0
Lip blister	3	2	0	0	1	1	0	0
Lip dry	3	2	0	0	1	1	0	0
Lip ulceration	3	2	0	0	1	1	0	0
Gingival pain	2	1	0	0	1	1	0	0
Glossodynia	2	1	0	0	0	0	0	0
Haematochezia	2	1	0	0	0	0	0	0
Abdominal discomfort	1	1	0	0	0	0	0	0
Anal fissure	1	1	0	0	0	0	0	0
Aphthous stomatitis	1	1	0	0	0	0	0	0
Chapped lips	1	1	0	0	1	1	0	0
Colitis	1	1	0	0	0	0	0	0
Epigastric discomfort	1	1	0	0	0	0	0	0
Gastritis	1	1	0	0	2	1	0	0
Gastrointestinal hemorrhage	1	1	0	0	0	0	0	0
Gastrointestinal pain	1	1	0	0	0	0	0	0
Gingivitis	1	1	0	0	2	1	0	0
Hiatus hernia	1	1	0	0	0	0	0	0
Mouth cyst	1	1	0	0	0	0	0	0
Oral mucosal exfoliation	1	1	0	0	0	0	0	0

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MedDRA Preferred Terms	Lapatinib + capecitabine AEs N = 164				Capecitabine AEs N = 152			
	All	%	G3-4	%	All	%	G3-4	%
Rectal hemorrhage	1	1	0	0	0	0	0	0
Retching	1	1	0	0	0	0	0	0
General disorders and administration site conditions								
Pain	5	3	1	1	3	2	1	1
Chills	3	2	0	0	4	3	0	0
Face edema	2	1	0	0	1	1	0	0
Impaired healing	2	1	0	0	0	0	0	0
Abasia	1	1	0	0	1	1	1	1
Axillary pain	1	1	0	0	3	2	0	0
Gait disturbance	1	1	0	0	1	1	1	1
Inflammation	1	1	0	0	1	1	0	0
Necrosis	1	1	0	0	0	0	0	0
Edema	1	1	0	0	1	1	0	0
Hepatobiliary disorders								
Hyperbilirubinemia	5	3	1	1	3	2	1	1
Hepatic function abnormal	2	1	1	1	0	0	0	0
Budd-Chiari syndrome	1	1	0	0	0	0	0	0
Cholecystitis	1	1	0	0	0	0	0	0
Hepatic pain	1	1	0	0	0	0	0	0
Hepatotoxicity	1	1	0	0	1	1	0	0
Jaundice	1	1	0	0	0	0	0	0
Immune system disorders								
Hypersensitivity	1	1	0	0	0	0	0	0
Infections and infestations								
Nasopharyngitis	7	4	0	0	10	7	0	0
Localized infection	6	4	0	0	2	1	0	0
Nail infection	6	4	1	1	3	2	0	0
Urinary tract infection	4	2	1	1	4	3	0	0
Oral candidiasis	3	2	0	0	0	0	0	0
Sinusitis	3	2	0	0	2	1	0	0
Upper respiratory tract infection	3	2	0	0	4	3	2	1
Bronchitis	2	1	0	0	2	1	0	0
Erysipelas	2	1	1	1	0	0	0	0
Infection	2	1	0	0	2	1	0	0
Influenza	2	1	1	1	1	1	0	0
Lower respiratory tract infection	2	1	0	0	1	1	0	0
Paronychia	2	1	0	0	1	1	0	0
Rhinitis	2	1	0	0	1	1	0	0
Skin infection	2	1	0	0	3	2	0	0
Tooth abscess	2	1	0	0	1	1	0	0
Viral infection	2	1	0	0	1	1	0	0
Catheter related infection	1	1	1	1	0	0	0	0
Cellulitis	1	1	1	1	0	0	0	0
Ear infection	1	1	0	0	0	0	0	0
Escherichia sepsis	1	1	1	1	0	0	0	0
Fungal rash	1	1	0	0	0	0	0	0
Fungal skin infection	1	1	0	0	0	0	0	0
Gastroenteritis	1	1	0	0	0	0	0	0
Genital infection fungal	1	1	0	0	0	0	0	0
Gingival abscess	1	1	0	0	0	0	0	0
Herpes simplex	1	1	0	0	3	2	0	0
Herpes zoster	1	1	0	0	0	0	0	0
Hordeolum	1	1	0	0	0	0	0	0
Lymphangitis	1	1	0	0	1	1	0	0
Pyelonephritis	1	1	0	0	0	0	0	0

MedDRA Preferred Terms	Lapatinib + capecitabine AEs N = 164				Capecitabine AEs N = 152			
	All	%	G3-4	%	All	%	G3-4	%
Sialoadenitis	1	1	0	0	0	0	0	0
Injury, poisoning and procedural complications								
Skin laceration	2	1	0	0	0	0	0	0
Back injury	1	1	1	1	0	0	0	0
Medical device complication	1	1	0	0	0	0	0	0
Rib fracture	1	1	0	0	0	0	0	0
Thermal burn	1	1	0	0	1	1	0	0
Wound	1	1	0	0	1	1	0	0
Investigations								
Blood bilirubin increased	7	4	1	1	1	1	0	0
Ejection fraction decreased	6	4	1	1	0	0	0	0
Alanine aminotransferase increased	4	2	0	0	2	1	0	0
Aspartate aminotransferase increased	4	2	1	1	3	2	0	0
Blood alkaline phosphatase increased	4	2	0	0	2	1	0	0
Haemoglobin decreased	4	2	0	0	2	1	0	0
Weight decreased	4	2	0	0	8	5	0	0
Blood albumin decreased	1	1	0	0	0	0	0	0
Blood bicarbonate decreased	1	1	0	0	0	0	0	0
Blood creatine increased	1	1	0	0	0	0	0	0
Blood phosphorus decreased	1	1	0	0	0	0	0	0
Cardiac murmur	1	1	0	0	0	0	0	0
Creatinine renal clearance decreased	1	1	0	0	0	0	0	0
International normalised ratio increased	1	1	1	1	0	0	0	0
Platelet count decreased	1	1	0	0	0	0	0	0
Respiratory rate increased	1	1	0	0	0	0	0	0
White blood cell count decreased	1	1	0	0	2	1	1	1
Metabolism and nutrition disorders								
Dehydration	7	4	3	2	7	5	2	1
Hypokalaemia	6	4	5	3	5	3	2	1
Decreased appetite	5	3	0	0	4	3	0	0
Acidosis	1	1	1	1	0	0	0	0
Hypercholesterolaemia	1	1	0	0	0	0	0	0
Hyperglycaemia	1	1	0	0	4	3	0	0
Hyperuricaemia	1	1	0	0	0	0	0	0
Hypoalbuminaemia	1	1	0	0	2	1	0	0
Hypocalcaemia	1	1	0	0	1	1	0	0
Hypochloraemia	1	1	0	0	0	0	0	0
Hyponatraemia	1	1	1	1	2	1	1	1
Hypoproteinaemia	1	1	0	0	0	0	0	0
Lactose intolerance	1	1	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders								
Muscle spasms	7	4	0	0	2	1	0	0
Myalgia	6	4	1	1	6	4	0	0
Musculoskeletal chest pain	3	2	0	0	5	3	0	0
Buttock pain	2	1	0	0	0	0	0	0
Neck pain	2	1	0	0	2	1	0	0
Arthritis	1	1	1	1	1	1	0	0
Joint stiffness	1	1	0	0	0	0	0	0
Muscular weakness	1	1	0	0	2	1	1	1
Musculoskeletal discomfort	1	1	0	0	0	0	0	0
Musculoskeletal stiffness	1	1	0	0	0	0	0	0
Osteonecrosis	1	1	1	1	0	0	0	0
Pain in jaw	1	1	0	0	1	1	0	0
Sensation of heaviness	1	1	0	0	0	0	0	0
Shoulder pain	1	1	0	0	3	2	0	0

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MedDRA Preferred Terms	Lapatinib + capecitabine AEs N = 164				Capecitabine AEs N = 152			
	All	%	G3-4	%	All	%	G3-4	%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)								
Acute myeloid leukaemia	1	1	1	1	0	0	0	0
Cancer pain	1	1	1	1	0	0	0	0
Malignant melanoma	1	1	1	1	0	0	0	0
Metastases to central nervous system	1	1	0	0	0	0	0	0
Metastatic pain	1	1	1	1	0	0	0	0
Neoplasm skin	1	1	0	0	0	0	0	0
Nervous system disorders								
Dizziness	7	4	0	0	13	9	2	1
Paraesthesia	5	3	0	0	8	5	0	0
Hypoesthesia	3	2	0	0	1	1	0	0
Neuropathy peripheral	3	2	0	0	5	3	0	0
Hyperaesthesia	2	1	0	0	1	1	0	0
Neuropathy	2	1	0	0	2	1	0	0
Peripheral sensory neuropathy	2	1	0	0	8	5	0	0
Balance disorder	1	1	0	0	1	1	0	0
Coordination abnormal	1	1	0	0	1	1	1	1
Dizziness postural	1	1	0	0	0	0	0	0
Dysaesthesia	1	1	0	0	1	1	0	0
3rd nerve paralysis	1	1	0	0	0	0	0	0
Neuralgia	1	1	1	1	1	1	0	0
Parosmia	1	1	0	0	0	0	0	0
Sensory disturbance	1	1	0	0	0	0	0	0
Somnolence	1	1	0	0	0	0	0	0
Spinal cord compression	1	1	1	1	0	0	0	0
Syncope	1	1	1	1	1	1	1	1
Psychiatric disorders								
Anxiety	7	4	1	1	3	2	0	0
Depression	4	2	2	1	4	3	0	0
Depressed mood	2	1	0	0	0	0	0	0
Attention deficit/hyperactivity disorder	1	1	0	0	0	0	0	0
Confusional state	1	1	0	0	0	0	0	0
Emotional disorder	1	1	0	0	0	0	0	0
Tearfulness	1	1	0	0	0	0	0	0
Renal and urinary disorders								
Dysuria	4	2	1	1	1	1	0	0
Nephrolithiasis	2	1	0	0	0	0	0	0
Pollakiuria	2	1	0	0	1	1	0	0
Bladder pain	1	1	0	0	0	0	0	0
Hydronephrosis	1	1	0	0	0	0	0	0
Reproductive system and breast disorders								
Breast pain	3	2	0	0	2	1	1	1
Vaginal hemorrhage	3	2	0	0	0	0	0	0
Genital pain female	1	1	0	0	0	0	0	0
Genital pruritus female	1	1	0	0	1	1	0	0
Genital tract inflammation	1	1	0	0	0	0	0	0
Pelvic pain	1	1	0	0	1	1	0	0
Vaginal discharge	1	1	0	0	3	2	0	0
Respiratory, thoracic and mediastinal disorders								
Pharyngolaryngeal pain	3	2	0	0	2	1	0	0
Rhinorrhoea	3	2	0	0	1	1	0	0
Asthma	2	1	1	1	0	0	0	0
Nasal ulcer	2	1	0	0	0	0	0	0
Pulmonary embolism	2	1	2	1	1	1	1	1
Bronchospasm	1	1	1	1	0	0	0	0

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MedDRA Preferred Terms	Lapatinib + capecitabine AEs N = 164				Capecitabine AEs N = 152			
	All	%	G3-4	%	All	%	G3-4	%
Dry throat	1	1	0	0	0	0	0	0
Dyspnoea exacerbated	1	1	0	0	0	0	0	0
Dyspnoea exertional	1	1	1	1	0	0	0	0
Haemoptysis	1	1	1	1	1	1	0	0
Nasal congestion	1	1	0	0	3	2	0	0
Nasal dryness	1	1	0	0	0	0	0	0
Pleural effusion	1	1	1	1	1	1	1	1
Productive cough	1	1	0	0	0	0	0	0
Rhinalgia	1	1	0	0	1	1	0	0
Rhinitis allergic	1	1	0	0	1	1	0	0
Skin and subcutaneous tissue disorders								
Dermatitis acneiform	7	4	1	1	0	0	0	0
Nail disorder	7	4	0	0	2	1	0	0
Pruritus	7	4	0	0	4	3	0	0
Alopecia	6	4	0	0	4	3	0	0
Skin hyperpigmentation	5	3	0	0	6	4	0	0
Onycholysis	3	2	0	0	1	1	0	0
Skin lesion	3	2	0	0	0	0	0	0
Blister	2	1	1	1	2	1	0	0
Hyperhidrosis	2	1	0	0	1	1	0	0
Ingrowing nail	2	1	0	0	1	1	0	0
Pain of skin	2	1	0	0	1	1	0	0
Palmar erythema	2	1	0	0	0	0	0	0
Rash macular	2	1	0	0	0	0	0	0
Skin chapped	2	1	0	0	2	1	0	0
Skin discolouration	2	1	0	0	1	1	0	0
Skin ulcer	2	1	1	1	1	1	0	0
Erythema multiforme	1	1	0	0	0	0	0	0
Exfoliative rash	1	1	0	0	2	1	1	1
Hair growth abnormal	1	1	0	0	0	0	0	0
Heat rash	1	1	0	0	0	0	0	0
Nail discolouration	1	1	0	0	0	0	0	0
Nail dystrophy	1	1	0	0	0	0	0	0
Nail toxicity	1	1	0	0	0	0	0	0
Onychoclasia	1	1	0	0	0	0	0	0
Rash erythematous	1	1	0	0	0	0	0	0
Rash pruritic	1	1	0	0	2	1	0	0
Skin disorder	1	1	0	0	0	0	0	0
Skin exfoliation	1	1	0	0	2	1	0	0
Skin fissures	1	1	1	1	0	0	0	0
Skin hypertrophy	1	1	0	0	0	0	0	0
Xeroderma	1	1	0	0	0	0	0	0
Dermatitis exfoliative	0	0	0	0	1	1	0	0
Hypoaesthesia facial	0	0	0	0	1	1	0	0
Pigmentation disorder	0	0	0	0	2	1	0	0
Rash generalised	0	0	0	0	1	1	0	0
Surgical and medical procedures								
Incisional drainage	0	0	0	0	1	1	0	0
Vascular disorders								
Hot flush	2	1	0	0	2	1	0	0
Lymphoedema	2	1	1	1	1	1	0	0
Hypotension	1	1	0	0	2	1	0	0
Vasodilatation	1	1	0	0	0	0	0	0

Source: Study EGF100151 study report.

10.1.2 Study EGF20002

This was an open-label, multicenter, single arm study of oral lapatinib in women with advanced or metastatic breast cancer whose disease had progressed while receiving trastuzumab containing regimens. The primary endpoints of the study was to evaluate the tumor response rate, complete response (CR) + partial response (PR) assessed by RECIST. The secondary endpoints including overall survival, clinical benefit, response duration, time to progression, 4-and 6-month progression free survival.

Major eligible criteria includes

- histologically or cytologically confirmed advanced (Stage IIIb) or metastatic (Stage IV) breast cancer
- Documented disease progression while receiving prior therapy with trastuzumab alone or in combination with other chemotherapy and must have received at least 6 weeks of standard doses of trastuzumab.

Subjects received 1250 mg lapatinib once daily (QD), following the morning meal. Subjects continued this treatment regimen until disease progression, consent withdrawal, or investigational product discontinuation due to unacceptable toxicity. In cases of drug-related toxicity, a dose reduction to 1000 mg/day was permitted. The protocol was subsequently amended (after 34 subjects had started receiving study medication) to increase the dose to 1500 mg lapatinib QD until disease progression or withdrawal from the study, with dose reduction to 1250 mg being permitted for drug-related toxicity. Forty-four subjects were enrolled after the protocol was amended and began treatment with lapatinib at 1500 mg QD.

Tumor response was evaluated every 8 weeks and at the end of study treatment. Subjects withdrawn from study treatment with stable disease were assessed every 8 weeks until disease progression. After disease progression, all subjects were followed at approximately 2-month intervals for survival until death. Best response to treatment was assessed objectively according to modified RECIST and was independently confirmed. The independent review panel was blinded to the response evaluations of the investigators.

The study was planned to enroll 80 subjects in order to have 90% power to detect a response rate of 15%. Due to the slow subject recruitment rate, enrollment was halted on 15 December 2004, at which time 78 subjects had been enrolled. At the time of the clinical cut-off date (1 June 2005) for reporting of the data, study EGF20002 was ongoing with 36 subjects still being followed for survival. The majority of subjects were white (76%) with a median age of 54 years. 99% of subjects had Stage IV disease at baseline and 85% of subjects had infiltrating ductal histology and 50% had liver metastases.

The study results showed that oral lapatinib 1250mg or 1500mg demonstrated modest activity when administered once daily as monotherapy for subjects with advanced or metastatic breast cancer that had progressed beyond trastuzumab-containing regimens. The tumor response rates (CR or PR) as

evaluated by the independent review panel and by the investigator were 5% and 8%, respectively. The percentage of subjects deriving clinical benefit (CR or PR or Stable Disease =24 weeks) was 9% (95% CI: 3.7, 17.6) as evaluated by the independent review panel and 14% (95% CI: 7.3, 23.8) as evaluated by the investigator. The median TTP was 15.3 weeks based on independent review and 9.0 weeks based on investigator review. The median overall survival time was 78.6 weeks. The probabilities of survival to 4 months and 6 months were 89% and 85%, respectively.

10.1.3 Study EGF 20008

This was a phase II open-label, two-cohort, multicenter study to evaluate the efficacy and toxicity of oral lapatinib administered to female subjects with refractory advanced (Stage IIIb) or metastatic (Stage IV) breast cancer. The primary endpoints of the study was to evaluate the tumor response rate, complete response (CR) + partial response (PR) assessed by RECIST. The secondary endpoints including overall survival, clinical benefit, response duration, time to progression, 4-and 6-month progression free survival, and quality of life by FACT-B.

Major eligibility criteria includes

- refractory to treatment with anthracycline, taxane and capecitabine-containing regimens
- Cohort A were to have ErbB2 overexpressing tumors (+2 by IHC and fluorescence in situ hybridization [FISH]+ or +3 by IHC) and were to be refractory to treatment with trastuzumab and Cohort B had non-ErbB2 overexpressing tumors.

Subjects received 1500 mg lapatinib orally QD one hour before or after the morning meal. Subjects continued this treatment regimen until disease progression, consent withdrawal, or investigational product discontinuation due to unacceptable toxicity. In cases of drug-related toxicity, dose reduction to 1250 mg/day was permitted.

Tumor response was evaluated every 8 weeks and at the end of study treatment. Best response to treatment was assessed objectively according to RECIST criteria and was independently confirmed. The independent review panel was completely independent of the subject management and was blinded to the response evaluations of the investigators.

Subjects with progressive disease were followed for survival at approximately 12-week intervals until death. Subjects with a complete response (CR), partial response (PR), or stable disease (SD) who discontinued investigational product administration due to an adverse event or unacceptable toxicity were assessed every 12 weeks until progression. Thereafter, subjects were followed for survival at approximately 12-week intervals until death. Subjects who discontinued investigational product and did not have a response were followed for survival after the end of investigational product administration approximately every 12 weeks until death.

The study was planned to enroll 200 evaluable subjects in this study (120 evaluable subjects in Cohort A and 80 evaluable subjects in Cohort B). Total 229 subjects were enrolled and treated with at least one dose of lapatinib (140 in Cohort A, 89 in Cohort B). At the time of the clinical cut-off

date (02 February 2005) for reporting of the data, study EGF20008 was ongoing with 90 subjects still being followed for survival.

Most subjects enrolled in this study were white (87%) and postmenopausal (80%); the median age was 53 years. Ninety-five percent of subjects had Stage IV disease, 83% had infiltrating duct histology, and more than half had bone (56%), liver (55%), or lymph node (52%) metastases.

In cohort A, the primary endpoint of the tumor response rate was 1% (2 PR) by independent review and 4% (3 CR, 3 PR) by investigator assessment. In cohort B, no responses were noted by either assessment. Using the independent assessment the median TTP was 9.1 weeks in Cohort A and 7.6 weeks in Cohort B, using the investigator assessment of TTP was 8.1 weeks and 7.0 weeks respectively. The median overall survival time was 29.4 weeks for subjects in Cohort A and 18.6 weeks for subjects in Cohort B, 6% of subjects in Cohort A had clinical benefit based on CR, PR or SD for ≥ 24 weeks per independent and investigator assessment. No subjects in Cohort B achieved clinical benefit on this basis by either review.

10.1.4 Study EGF 10005

This was an open-label, multiple-dose, dose-escalation study of oral lapatinib and oral capecitabine given in combination to male and female subjects with histological confirmed, advanced solid tumors, with a life expectancy of more than 12 weeks. The primary endpoints were:

- The safety and tolerability endpoints consisted of the evaluation of adverse events (AEs), and changes in vital signs and laboratory values.
- A dose regimen where no more than 1 out of 6 subjects had a dose-limiting toxicity (DLT) was defined as the OTR.

Secondary endpoints were:

- To assess the clinical activity, tumor response, of lapatinib administered in combination with capecitabine by RECIST.
- To determine the pharmacokinetic (PK) profile of lapatinib and capecitabine (and 5-FU) when administered alone and in combination.

Subjects received capecitabine for 14 days on a 21-day cycle, administered on the standard twice daily schedule. In addition, lapatinib was administered once daily for the entire duration of the study. The starting doses of lapatinib and capecitabine were 1250 mg/day and 1500 mg/m²/day (750 mg/m² twice daily (BID)), respectively. At least 3 subjects were to be entered at this dose level and monitored for toxicity. Subjects could be enrolled simultaneously in the cohort. If no dose-limiting toxicity (DLT) was observed, a further 3 subjects were to be entered at the next higher dose level [level +1: lapatinib 1250 mg/day and capecitabine 2000 mg/m²/day (1000 mg/m² BID)] and so on until DLT was observed or the maximum dose level was reached in the absence of DLT.

Planned doses of lapatinib ranged between 750 mg/day and 1500 mg/day. Planned doses of capecitabine ranged from 1500 to 2500 mg/m²/day (750 to 1250 mg/m² BID).

It was planned to enroll 50 subjects into the study. Total 45 subjects were enrolled into three cohorts. In the dose escalation phase, 18 subjects were treated to determine the OTR (Cohort 1). After establishment of the OTR, 3 subjects were treated to evaluate the tolerability of the combination with a higher capecitabine dose and 3 subjects were treated to further evaluate the safety of the OTR (Cohort 2). In the pharmacokinetics phase, 21 subjects were treated at the OTR to evaluate the pharmacokinetic profiles of the study combination (Cohort 3). Twenty-three (51%) of the 45 subjects were female and 22 subjects were male (49%).

The majority of the subjects enrolled were white (71%) and had a median age of 58.3 years. Colon (8 subjects), lung (8 subjects) and breast (7 subjects) were the most frequent primary sites of disease. About 53% of subjects had received at least 2 prior cancer chemotherapy regimens. The OTR was lapatinib 1250 mg/day + capecitabine 2000 mg/m²/day (1000 mg/m² BID).

10.1.5 Efficacy Summary of Other Supportive Studies

See section 6.1.5.

10.1.6 Safety Summary of Supportive Studies

Of 307 subjects enrolled in Study EGF20002 and Study EGF20008, 34 received lapatinib 1250mg and 273 received lapatinib 1500mg. In these studies, lapatinib monotherapy in Study EGF20002 and Study EGF20008 was discontinued by all subjects at the 1250mg dose (Study EGF20002 only) and almost all subjects (96%) at the 1500mg dose.

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

Table 102: Common AEs (≥5%) in studies EGF20002 and EGF 20008 regardless treatment relationship

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

Source: Study EGF20002 and 2008 reports.

1. Diarrhea included diarrhea, loose stools, and frequent bowel movements.
2. Rash included acne, erythema, eczema, rash papular, dermatitis, rash, folliculitis, and rash pustular.

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

Table 103: Serious AEs in studies EGF20002 and EGF 20008 regardless treatment relationship

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

Source: Study EGF20002 and 2008 reports.

The most common reason for discontinuation of treatment was disease progression. This pattern was observed regardless of age group. There were no notable differences in discontinuations based on race; however, the limited number of non-whites limits firm conclusions based on race. Overall, 7% of subjects withdrew due to AEs.

Table 104: Analyses on study drug discontinuation

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

Source: Study EGF20002 and 2008 reports.

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

Table 105: Deaths within 30 Days of Last Dose – Studies EGF20002 and EGF20008

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

Source: Study EGF20002 and 2008 reports.

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

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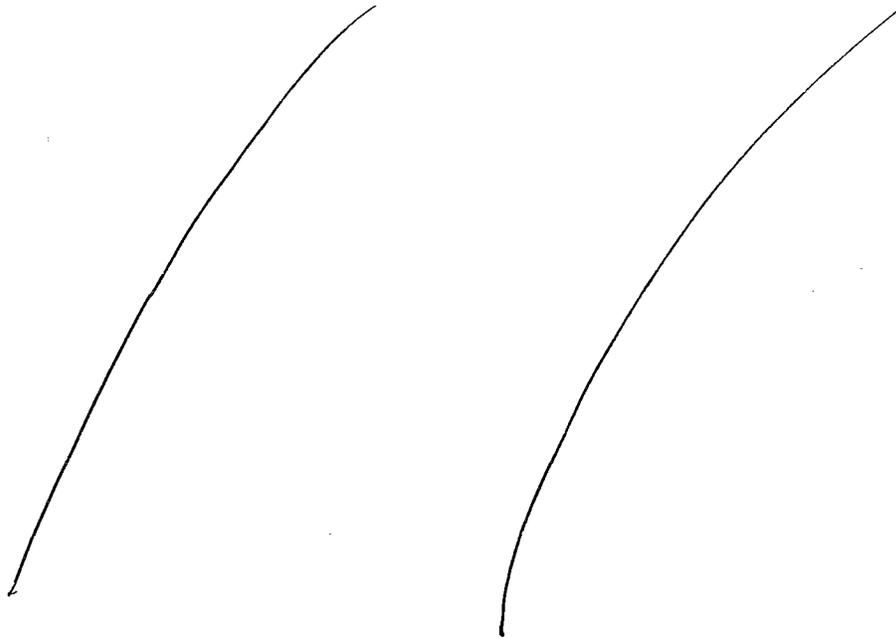
Table 106: Fatal Adverse Events - Studies EGF20002 and EGF20008

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

Source: Study EGF20002 and 2008 reports.

10.2 Line-by-Line Labeling Review

The multidisciplinary team review/edited label is shown as below. Please also see approved label for the final version.



24 Page(s) Withheld

 Trade Secret / Confidential

✓ Draft Labeling

 Deliberative Process

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/s/

Qin Ryan
3/13/2007 10:23:03 AM
MEDICAL OFFICER

Amna Ibrahim
3/13/2007 10:51:26 AM
MEDICAL OFFICER

**Interdisciplinary Review Team for QT Studies
Response to a Request for Consultation: NDA Review**

NDA	22059
Brand Name	TYKERB™
Generic Name	Lapatinib
Sponsor	GlaxoSmithKline
Indication	Treatment of patients with advanced or metastatic breast cancer in combination with capecitabine
Dosage Form	Tablets for oral administration
Therapeutic Dose	1250 mg once daily
Duration of Therapeutic Use	Administered daily until disease progression or unacceptable toxicity
Maximum Tolerated Dose	Not established (highest dose given=1800 mg QD)
Application Submission Date	26-Aug-2006
Review Classification	Other
Date Consult Received	3-Oct-2006
Date Consult Due	15-Nov-2006
Clinical Division	Division of Drug Oncology Products
PDUFA Date	13-Mar-2007

1.0 RECOMMENDATION

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

Under Clinical Pharmacology:

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

Under Precautions or Warnings:

Lapatinib should be administered with caution to patients who have or may develop prolongation of QTc. These conditions include patients with hypokalemia or hypomagnesemia, with congenital long QT syndrome, patients taking anti-arrhythmic medicines or other medicinal products that lead to QT prolongation, and cumulative high-dose anthracycline therapy. Hypokalemia or hypomagnesemia should be corrected prior to lapatinib administration.

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

2.0 SUMMARY OF FINDINGS

The QT prolongation potential of lapatinib was assessed as part of a phase 1 dose escalation study of lapatinib in advanced cancer patients. Eighty-one (81) patients received daily doses of lapatinib ranging from 175 mg/day to 1800 mg/day. Serial ECGs were collected on day 1 and day 14 to evaluate the effect of lapatinib on QT intervals.

Review of the QT data indicates that lapatinib prolongs the QTc interval.

- A total of 13 (of the 81) subjects were found to have either a QTcF duration > 480 msec or a QTcF prolongation of > 60 msec. According to the Sponsor, "independent review indicated that none of these abnormalities were clinically significant." However, the sponsor did not submit ECGs for review and this statement could not be confirmed.
- The maximum mean change from baseline across dose groups (175 mg QD to 1800 mg QD and 900 mg BID) ranged from 10 to 39 msec; however, there was no dose-response relationship. This could be due to lack of a placebo group, time-matched baseline, and small numbers of patients within each dose group.
- A significant relationship between lapatinib concentration and the QTcF interval was found. At the mean peak concentration (C_{max}) of 3203 ng/ml following the 1250 mg daily dose, the predicted change in QTcF was estimated to be 13.5 msec. with an upper confidence interval of 22.4 msec. Co-administration of CYP3A4 inhibitors, administration of drug with food, or administration to patients with hepatic impairment, could further prolong the QTc interval.

The Sponsor did not submit related ECGs to the ECG warehouse; consequently, we are unable to verify that the QT measurements were made appropriately.

3.0 GOAL OF THE REVIEW

The purpose of this review is to assess the impact of lapatinib on QT interval based on information provided in the submission.

4.0 BACKGROUND

4.1. Indication

Lapatinib, in combination with capecitabine, is indicated for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 (ErbB2)

4.2. Drug Class

Tyrosine kinase inhibitor: dual kinase inhibitor of ErbB1 and ErbB2.

4.3. Market approval status

This drug is not approved for use for any indication in the United States, nor is approved for use for any indication in any other country.

5.0 DRUG INFORMATION

5.1. Preclinical Information

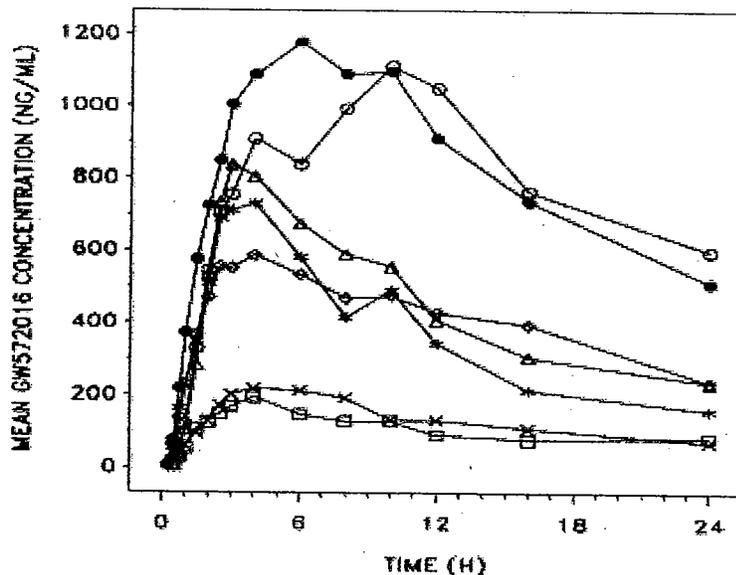
Lapatinib works intracellularly and directly targets the tyrosine kinase (TK) domain of ErbB1 and ErbB2. Lapatinib binds reversibly to the cytoplasmic adenosine triphosphate (ATP)-binding site of the kinase and blocks receptor phosphorylation and activation, thereby preventing subsequent downstream signaling events leading to tumor growth inhibition and apoptosis. Such a dual inhibitor should be useful for patients with tumors that express either or both growth factor receptors.

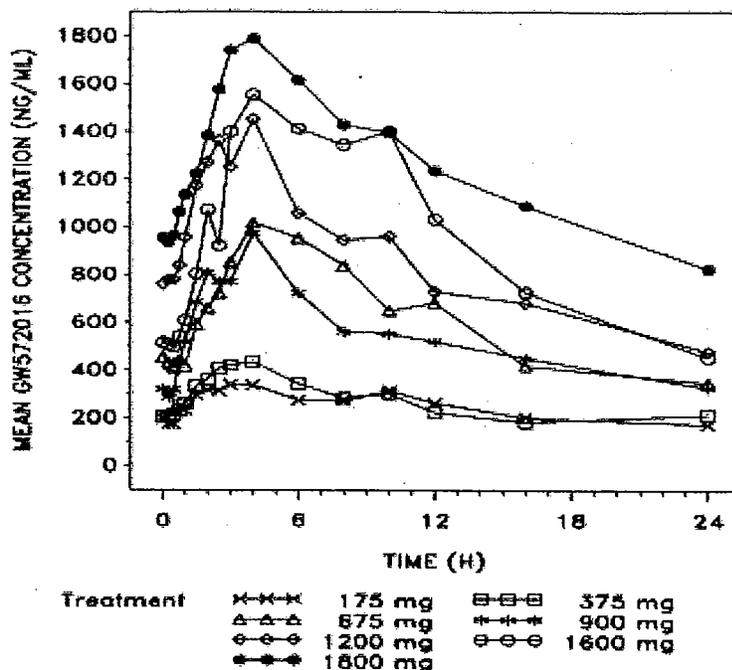
No treatment-related effects were noted on action potential parameters in isolated canine cardiac Purkinje fibers following treatment with lapatinib at concentrations up to 2560 ng/mL. In addition, no direct chronotropic effects were noted in isolated guinea pig field stimulated atria and there were no treatment-related effects electrocardiographic effects in conscious telemetered dogs at doses up to 500 mg/kg or in repeat dose studies of up to 9 months duration in the dog at C_{max} and AUCs that were up to 2-fold the expected human exposure.

5.2. Clinical Pharmacology

The following figure illustrates the pharmacokinetics of lapatinib following escalating doses on day 1 and day 14 of multiple dosing.

Figure 1: Concentration-Time profile for lapatinib following escalating doses on day 1 (upper panel) and day 14 (lower panel).





The following table summarizes the key features of the clinical pharmacology of lapatinib.

Table 1: Highlights of Clinical Pharmacology of Lapatinib

Therapeutic dose	1250 mg once daily administered in combination with capecitabine. Drug is to be administered at least 1 hr before or after meals	
Maximum dose tested	Single Dose	250 mg in healthy subjects
	Multiple Dose	1800 mg QD in advanced cancer patients
Exposures Achieved	1800 mg QD (highest dose tested in study 10003)	Day 1 C _{max} = 1346 ng/ml (95% CI: — ng/ml) Day 14 C _{max} = 1888 ng/ml (95% CI: — ng/ml)
	1200 mg QD	Day 1 C _{max} = 763.2 ng/ml (95% CI: — ng/ml) Day 14 C _{max} = 1389 ng/ml (95% CI: — ng/ml)
	1250 mg QD (given with capecitabine in study 10005)	(steady-state) C _{max} = 3203 ng/ml (95% CI: — ng/ml)
Maximum tolerated dose	Not established. Highest dose administered was 1800 mg QD. Higher doses could not be given due to pill burden	
Principal adverse events	rash, nausea, fatigue, diarrhea, constipation, anorexia	
Absorption	Absolute	Not determined

	Bioavailability	
	Tmax	4 hrs
Distribution	Vz/F	Not reported
	% bound	>99%
Elimination	Route	<ul style="list-style-type: none"> Primarily hepatic metabolism, primarily by CYP3A4/5 Renal excretion <2% of dose
	Terminal t _{1/2}	<ul style="list-style-type: none"> 6 – 12 hrs (from single dose study in healthy subjects) Half-life appeared to increase with dose following single doses in healthy subjects
	CL/F	Not reported
	Accumulation: AUC _{24 (Day 14)} AUC _{24 (Day 1)}	<ul style="list-style-type: none"> 1.3 – 2.4 across doses following QD dosing
Range of linear PK	Dose proportional increases in AUC: 25 to 1250 mg single doses in healthy subjects	
Intrinsic Factors	Age	No apparent age effects based on review of data across studies
	Sex	No apparent sex effects based on review of data across studies
	Race	Not evaluated
Extrinsic Factors	Drug interactions	<ul style="list-style-type: none"> Extensively metabolized by CYP3A4/5 so PK may be affected by inhibitors or inducers DDI study with ketoconazole (CYP3A4 inhibitor) showed 3.6-fold increase in AUC of lapatinib in presence of ketoconazole. DDI study with carbamazepine (CYP3A4 inducer) showed 72% decrease in AUC of lapatinib in presence of carbamazepine
	Food Effects	<ul style="list-style-type: none"> 3-4 fold increase in exposure when given with meals Product label: to be taken one hour before or after meals
High Clinical Exposure scenario	<ul style="list-style-type: none"> Expected if co-administered with CYP3A4 inhibitors Expected in hepatic impairment (study indicated 56% and 85% increases in AUC in subjects with moderate and severe hepatic impairment respectively) Expected if lapatinib is given with food 	

Table 2: Peak concentrations at steady-state following daily lapatinib administration in two studies. Note that the 1250 mg QD in combination with capecitabine is the regimen used in the confirmatory trials and is the recommended dosing regimen in the label.

	Arithmetic Mean SD (%CV)	Geometric Mean 95% CI
STUDY 10003		
1200 mg QD (single agent) Day 14	1546 866 (56%)	1389 (749-2574)
STUDY 10005		
1250 mg QD (single agent)	3329 2521 (76%)	2431 (1570-3767)
1250 mg QD in combination w/ capecitabine	3699 1819 (49%)	3203 (2395-4284)

6.0. SPONSOR'S SUBMISSION

6.1. Overview

The Sponsor did not conduct a thorough QT study to assess the impact of lapatinib on QT interval.

The Sponsor submitted an exploratory analysis of ECGs collected during a Phase 1 open-label, multiple-dose, dose-escalation safety study in cancer patients following multi-day doses of lapatinib from 175mg to 1800mg/day (Study EGF10003).

The Sponsor also evaluated ECGs collected during two phase I studies of single and multiple escalating doses of lapatinib in healthy subjects. Following single doses of 10 to 250 mg of lapatinib and daily dosing (for up to 8 days) of 25 mg to 175 mg/day of lapatinib in healthy subjects, there were no clinically significant changes in ECG data that were related to lapatinib exposure (NOTE: the IRT has not reviewed the ECGs).

6.2. Study Design(s)

6.2.1. Phase 1 Safety Study (Study EGF10003)

6.2.1.1. Synopsis

6.2.1.1.1. Title: A Phase I, Open-Label, Multiple Dose, Dose-Escalation Study of GW572016 in Patients with Solid Tumors.

6.2.1.1.2. Protocol Number: EGF10003.

6.2.1.1.3. Objectives:

Primary Objective:

- Determine the maximum tolerated dose (MTD) and safety of oral lapatinib following once daily dosing in cancer subjects.
- Evaluate the pharmacokinetics of oral lapatinib following once daily dosing in cancer subjects.

- To evaluate the pharmacokinetics of oral lapatinib following twice daily dosing in cancer subjects (Amendments 04 and 07).
- To evaluate the pharmacokinetics of oral lapatinib following fed and fasted once daily dosing in cancer subjects (Amendment 06).

Secondary Objective:

- To evaluate, by qualitative immunohistochemistry (IHC), biomarkers that are downstream from tyrosine auto-phosphorylation (e.g., ki67-proliferation marker, STAT-proliferation marker, and cyclin D- proliferation marker) from pre-treatment and post-treatment punch skin biopsies and/or buccal swabs.

Post-hoc objective

- In addition to the planned objectives, post-hoc nonlinear and linear mixed-effects modeling of the QT interval data collected in this study was carried out to determine whether there was any potential QT effect related to lapatinib administration.

6.2.1.2. Design

6.2.1.2.1. Description: The overall protocol was an open-label, multiple-dose, dose-escalation study of oral lapatinib given once daily for 14 days (pharmacokinetic/pharmacodynamic phase) to male and female subjects, 18 years or older, with solid tumors that were amenable to treatment.

6.2.1.2.2 Population: The study enrolled eighty-one (81) male and female subjects with advanced solid tumors.

6.2.1.2.3. Treatment groups: The study included groups of 3-6 patients that received escalating daily doses of lapatinib for 14 days. The starting dose was 175 mg QD, and additional dose groups included 375 mg QD, 675 mg QD, 900 mg QD, 1200 mg QD, 1600 mg QD and 1800 mg QD. An additional cohort received 500 mg BID, 750 mg BID, and 900 mg BID.

6.2.1.2.4. Justification for dose provided: The starting dose of 175 mg/day was the highest dose tested in healthy subjects in an earlier study. Escalating doses were evaluated to examine the safety and determine the maximally tolerated dose of lapatinib in cancer patients.

6.2.1.2.5. Instructions with regard to meals: On days 1 and 14, subjects were required to fast for 2 hours before dosing to 4 hours post-dosing, with the exception of water, which was allowed freely except for 1 hour either side of dosing. During Days 2 through 13, subjects were required to fast from 2 hours before to 1 hour after each dose (with the exception of water which was allowed freely).

6.2.1.2.6. Study Schedule and Timing of Samples

Table 3. Highlights of Schedule of Interventions

Study Day	1	2-13	14
Intervention	First Dose	Daily dosing	Daily dose
12-Lead ECGs	Record ECGs [#]	None recorded	Record ECGs [#]
PK Samples	Collected ^{##}	None collected	Collected ^{##}
Meal Instructions	Fast from 2 hrs before to 4 hrs after dosing	Fast from 2 hrs before to 1 hr after dosing	Fast from 2 hrs before to 4 hrs after dosing

[#] predose (x3), 2, 4, 6, 8, 12, 16 and 24 hrs postdose

^{##} predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16 and 24 hrs postdose

Sponsor's justification for sampling schedule: No specific justification was provided for the sampling schedule. The intensive PK sampling was presumably to adequately characterize the PK of lapatinib, and the ECG sampling was to adequately evaluate any effect of lapatinib on QT interval.

6.2.1.2.7. QT Measurement: Continuous ECG monitoring was performed at 1 hour prior to and for 8 hours after study drug dosing on Days 1 and 14. Twelve-lead ECGs were obtained per Table 3 (above).

6.2.1.2.8. Controls: There was no control group in this study.

6.2.1.2.9. Blinding: This was an open-label study.

6.2.1.2.10. Baseline: ECGs were collected in triplicate (within 1 hr) prior to initiating dosing (on day 1).

6.2.1.2.11. Safety assessments: AEs were assessed throughout the study. Adverse events were graded according to the NCI-CTC, Version 2 (2003).

6.2.1.2.12. Vital Signs: Heart rate and blood pressure were recorded at the scheduled times on safety and pharmacokinetic assessment on Days 1 and 14 with the patient lying semi-recumbent position, having rested for at least 10 minutes before each reading. Three pre-dose measurements of blood pressure and heart rate were performed. After dosing, blood pressure and heart rate were measured at the following times: 30 minutes, 60 minutes, and 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16 and 24 hours.

6.3. Results

The following table highlights available data. Serial ECGs were collected on all patients on day 1 and day 14.

Table 4: Number of subjects included in study, by dose group.

Daily Dose (mg)	Number of Subjects	
	Study Day 1	Study Day 14
Cohort 1 (QD) (n=33):		
175	3	3
375	3	3
675	4	4
900	4	4
1200	6	6
1600	4	4
1800	9	9
Cohort 2 (BID) (n=41):		
500	13	13
750	22	20
900	6	5
Cohort 3 (Fed/Fasted) (n=7):		
1250	7	7

Sponsor's Statistical Analysis

No formal statistical analysis of the ECG data was conducted. Review of the QT data indicated that 13 (of the 81) subjects were found to have either a QTcF duration > 480 ms or a QTcF prolongation of > 60 ms (see Table 5, below). According to the Sponsor, independent review indicated that none of these abnormalities were clinically significant.

Table 5. Subjects with QTcF > 480 ms or Increased > 60 ms from Pre-dose.

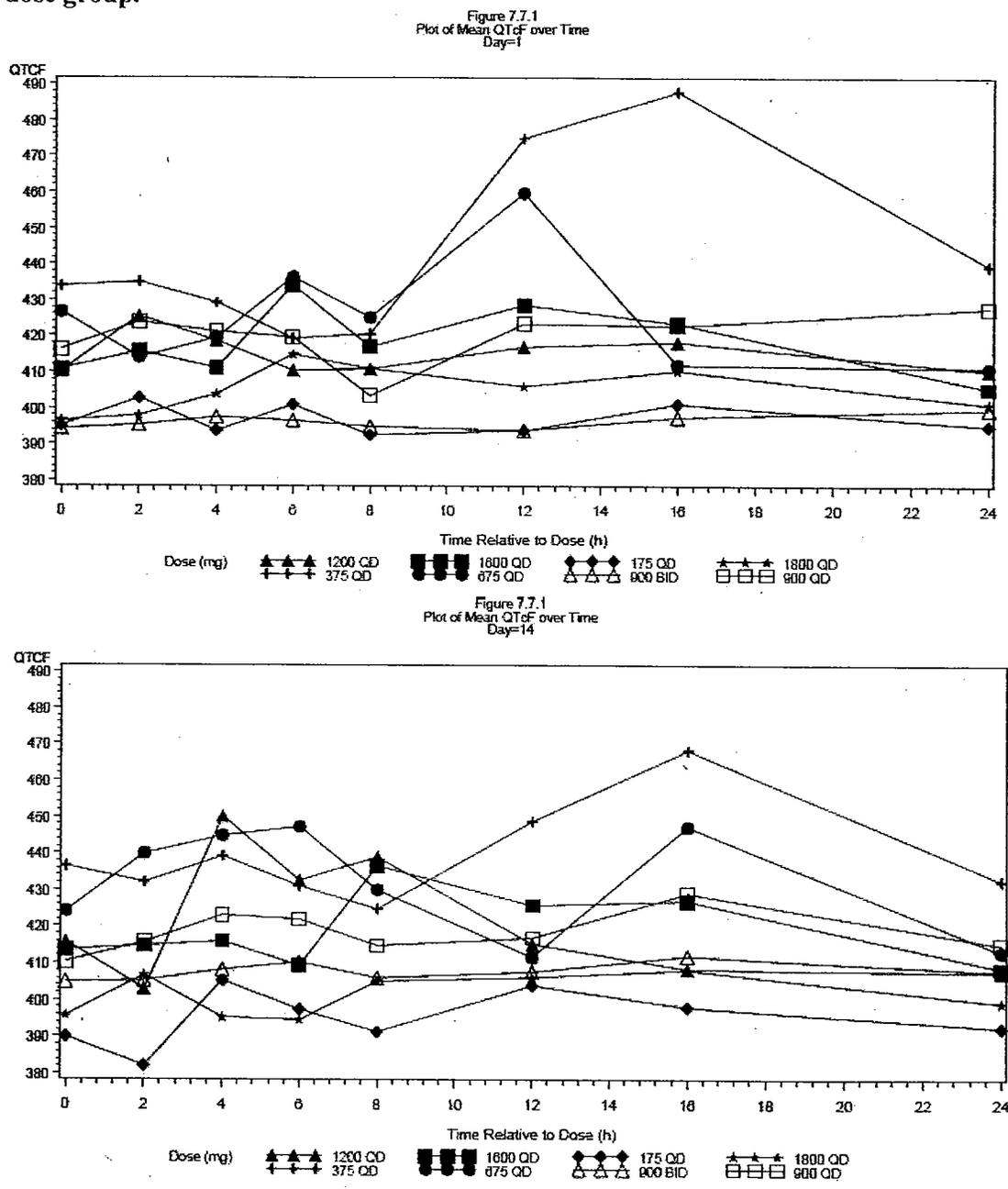
Subject No. / Cohort	Dose (mg)	Day/Hour of Max Value	Max Value	Change from pre-dose to Max	Last value ^a
104/1	375	14/16	525	66	442
105/1	375	2/24	488	43	463
107/1	675	14/12	493	27	461
108/1	675	1/12	471	65	395
		14/2	492	59	
115/1	1600	1/6	478	79	392
116/1	1600	14/8	529	100	457
118/1	1800	14/12	506	99	387
142/2	500 BID	14/0	494	NA	454
201/1	675	14/16	428	73	391
203/1	1200	14/4	536	112	492
207/1	1800	1/8	517	89	409
209/1	1800	1/24	436	61	375
252/1	1200	14/0	491	NA	456

a. Last value indicates ECG obtained when subject was taken off study. Source: Sponsor's table 31 (EGF10003). It should be noted that some of these subjects had received prior anthracycline, trastuzumab and/or mediastinal radiation therapy.

The following figure 2 shows the mean QTcF vs. time by dose group on day 1 and day 14.

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Figure 2: Mean QTcF over time for day 1 (upper panel) and day 14 (lower panel) by dose group.



Sponsor's Exposure-Response Analysis

Two analyses were performed by the sponsor to evaluate concentration – QT relationships on the data from study EGF10003:

Two analyses were performed: 1) non-linear mixed effects modeling of QT interval vs. concentration, and 2) linear mixed effects modeling of QTcF vs. concentration.

1) Non-linear mixed-effects modeling was used to determine whether lapatinib serum concentrations had any effect on QT interval duration. The sponsor modeled the individual heart-rate correction factor and effect of concentration simultaneously using all the data, which meant that the estimation of the heart-rate correction factor could be confounded by the effect of the drug on heart-rate (see reviewer's comment below).

The analysis was restricted to the complete or near complete datasets spanning 24 hours on each of 2 days available from 32 subjects in the 175 mg to 1800 mg daily dose cohorts and 6 subjects in the 900 mg twice daily cohort. Appendix 1 shows the distributions of QTcF data for the complete dataset (n=81 subjects) as well as the subset of the data used in the exposure-response analysis (n=38 subjects). The distributions are similar indicating that results of the analysis in the subset can be extrapolated to the complete dataset. Placebo data were not available to assess underlying sources of variability,

Base model:

$$QT = \theta_1 \cdot RR^{\theta_2} \cdot e^{\eta_1} + \varepsilon_1$$

where θ_1 = baseline individual-RR-corrected QT; θ_2 = alpha, the exponent; η_1 = proportional error term for between-subject variability (BSV); ε_1 : residual variability.

Additional linear terms were added to this base model to assess the effect of lapatinib dose, Cmax, Cmax/tmax (representing the rate of rise in concentration), and lapatinib concentration at the time of ECG recording, each associated with an additive term for BSV.

$$QT = \theta_1 \cdot RR^{\theta_2} \cdot e^{\eta_1} + \theta_3 \cdot \text{conc} + \eta_2 + \varepsilon_1$$

where θ_3 = slope of QT-conc relationship and η_2 = additive error term for between-subject variability.

Six other covariates added to the model included body mass index (BMI), age, sex, the number of concomitant medications (0, 1, 2) suspected or reported to prolong QT interval (levofloxacin, fluconazole, azithromycin, granisetron, and ondansetron), prior exposure to doxorubicin or trastuzumab, and the presence of a cardiac abnormality diagnosed by an independent cardiologist reviewing ECG from 16 subjects with QTcF intervals >480 ms or prolongations >60 ms (premature ventricular contraction, left anterior hemi-block, and a flat or inverted T-wave).

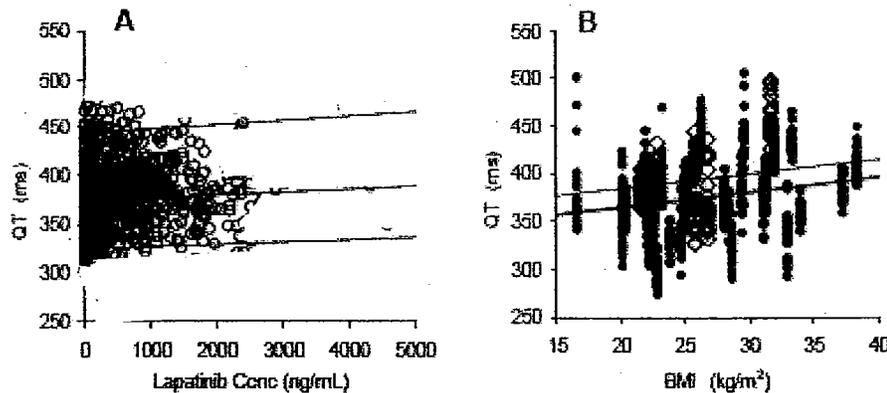
Results: There was a significant effect of lapatinib concentration on QT. The covariates that showed significant effects included BMI and prior exposure to doxorubicin or trastuzumab. The following table shows the final model parameter estimates.

Table 6: Final model parameter estimates for the non-linear mixed-effects modeling of QT interval data performed by the sponsor.

Final Model Parameter	Mean \pm SE [95% CI]	ω (BSV)
θ_1 (QTcI, corrected baseline)	406 \pm 3 [400 – 412]	2.66 \times 10 ⁻³ (5%)
θ_2 (α , heart rate correction factor)	0.347 \pm 0.02 [0.307 – 0.386]	
θ_3 (SL1, concentration coefficient)	0.0032 \pm 0.0014 [0.0005 – 0.0060]	1.86 \times 10 ⁻⁵ (136%)
θ_4 (SL2, BMI coefficient)	1.52 \pm 0.48 [0.56 – 2.48]	
θ_5 (SL3, prior med use slope)	19 \pm 5 [8 – 29]	
σ (residual variability)	258 \pm 45 ms	ε (WSV) = 16 msec

The following figure (figure 3) shows the QT interval vs. lapatinib concentration (left panel) and BMI (right panel). Also plotted are the model-predicted curves as described in the legend of the figure.

Figure 3. QT interval duration (A) vs lapatinib concentration with model-simulated slope and 90% CI, and (B) vs BMI with model-simulated slope (heavy line) plus the effect of prior exposure to adriamycin/trastuzumab (light line, open diamonds)



The following table (sponsor's table 2) shows the model-predicted QT prolongations computed by the sponsor under various conditions, including peak concentrations achieved following different exposures of lapatinib in study EGF10003.

Table 7: Model predicted QT interval prolongations, estimated from sponsor's model.

Contributing factors	Population model parameters	Predicted QT prolongation
1200mg QD mean Cmax = 1230 ng/mL	Mean SL ₁ = 0.0032	4 ms
1200mg QD highest Cmax = 2990 ng/mL		9 ms
900mg BID highest Cmax = 5663 ng/mL		18 ms
1200mg QD highest Cmax = 2990 ng/mL	95 th percentile SL ₁ = 0.0060	18 ms
Maximum observed BMI in study = 38 kg/m ²	Mean SL ₂ = 1.52 ± 0.5	19 ms
Prior exposure to adriamycin / trastuzumab	Mean SL ₃ = 19 ± 5	19 ms

2) Linear mixed effects modeling of QTcF vs. concentration.

It was of interest to determine whether there were any statistically significant effects of lapatinib concentration on QTcF duration after adjusting for other covariates that may affect QTcF.

Model:

$$QTcF = a + b1 \cdot \text{conc}$$

Subject was included as a random effect in the model since there were repeated observations for each subject. Assuming random variation between subjects allows for more flexibility in the model in that each subject contributes their own parameter estimates.

Covariates evaluated (as fixed effects) included age, gender, body mass index, and prior exposure to adriamycin and trastuzumab. Prior exposure to adriamycin and trastuzumab was of interest because these agents alter cardiac contractility. This term was set to 0 for subjects that did not receive either agent, 1 for subjects that received one but not both agents, and 2 for subjects that received both agents.

Results:

Lapatinib concentration, BMI, and prior exposure to medications were statistically significant at alpha=0.05. The following table (table 8) shows the final model parameter estimates.

Table 8: Linear mixed-effects modeling of QTcF interval durations: final model parameters.

Parameter	Slope Estimate	Standard Error	Degrees of Freedom	T-value	P-value
Intercept	364.72	20.48	35	17.81	<0.0001
Concentration	0.0028	0.0014	524	2.10	0.04
BMI	1.60	0.75	524	2.13	0.03
Prior meds	18.01	7.28	524	2.47	0.01

7.0. REVIEWERS' ASSESSMENT

7.1 Comments on Study Design

Adequacy of Exposure: The effect of lapatinib on QT intervals was evaluated across a almost 10-fold range of doses (175 to 1800 mg QD) and also following BID dosing. The recommended dose in the label is 1250 mg QD, which was within the range of doses evaluated in the study.

Adequacy of sampling: Based on the PK of lapatinib and planned dosing regimen, sampling for PK and ECG data on day 1 and 14 were adequate.

Adequacy of Controls: The primary objective of this study was to evaluate the safety and PK of escalating dose regimens of lapatinib in advanced cancer patients. There was no placebo group and there was no positive control group. Thus, some caution may be necessary in the interpretation of the results.

7.2 Reviewer's Analysis

- In the initial descriptive analysis, the sponsor has shown the mean QTcF vs. time for each of the dose groups but not calculated the upper 95% confidence interval to determine if it exceeds the 10 msec cutoff per ICH guidelines.
- Non-linear mixed-effects modeling of QT interval data indicated a statistically significant but small effect of lapatinib serum concentration on QT interval duration. However, between-subject variability in the slope was substantial. Other factors possibly contributing to the variability include the absence of a placebo and other controls on subject activity.
- The sponsor's non-linear mixed-effects analysis was performed using the uncorrected QT interval as the dependent variable and modeling the heart-rate correction factor and baseline corrected interval simultaneously with the effect of drug concentration and other covariates. Typically the heart-rate (RR interval) correction factor is estimated from data under placebo (no drug) conditions to avoid any confounding influences of the drug itself on RR interval. The data from the current study does not include a placebo arm, which could result in less reliable and biased estimates of the heart-rate correction factor.
- Linear mixed-effects modeling of the QTcF interval data also showed a significant but small effect of lapatinib serum concentration on QTcF.
- However, the sponsor's model did not appear to include estimation of the between-subject variability in the intercept and slope of the model (only random variation for subject was included).
- The dataset used by the sponsor did not include the baseline (day 1 time 0) QTcF data for any of the subjects. No explanation for this was provided.

- The inclusion of prior history of doxorubicin and/or trastuzumab was coded as a multinomial variable with a value of 0 for patients with no prior history, a value of 1 for patients who had used one of the medications and a value of 2 for patients who had used both medications previously. Again, no clear rationale for this was provided. Also, patient 208 had a prior history of doxorubicin treatment but was coded as 0 for prior medication use.

Reviewer's Descriptive Analysis

For each dose group, the mean change in QTcF interval on day 14 (change from day 1 baseline) was computed. The maximum change in QTcF interval for each dose group is tabulated below in table 9. The table indicates that there is no apparent dose-response relationship. This could be due to lack of a placebo group, time-matched baseline, and small numbers of patients within each dose group. Figure A 1.1 in the appendix shows the Delta QTcF vs. time plots on day 14 for each patient by dose group. Figure A 1.2 in the appendix shows the concentration vs. time plots for each patient by dose group. An evaluation of the mean lapatinib concentration -time and QTcF-time relationship indicated that there was no time-delay or hysteresis.

Table 9: Maximum change in mean and median QTcF intervals on day 14 for each dose group.

Dose Group	Number of subjects	Maximum change in Mean QTcF (msec)	Time of maximum change in Mean QTcF (hrs)	Maximum change in Median QTcF (msec)	Time of maximum change in Median QTcF (hrs)
175 mg QD	3	10.1	4	7.9	4
375 mg QD	3	34.3	16	38.0	16
675 mg QD	4	20.6	8	21.1	8
900 mg QD	4	12.6	8	12.8	8
1200 mg QD	5	38.6	4	19.5	4
1600 mg QD	4	25.6	8	18.4	8
1800 mg QD	9	11.6	12	8.6	12
900 mg BID	6	17.6	2	17.4	2

Reviewer's Exposure-Response Analysis

The reviewer re-analyzed the QTcF – concentration data from the study using linear mixed-effects modeling in SAS (version 9, Cary, NC). The dataset (n=38 subjects, 600 observations) analyzed by the reviewer included the day 1 time 0 data for all subjects. Also, the prior use of doxorubicin and/or trastuzumab was coded as a binomial variable (0 if no prior use and 1 if prior use of one or both medications), and prior medication use was coded as 1 for patient 208.

The effect of lapatinib concentration along with several covariates, BMI, and prior exposure to adriamycin and trastuzumab was examined. The effect of gender was examined as an independent effect and as an interaction with concentration. Random variations in intercept and slope were also included in the model as additive effects (SAS code for PROC MIXED included in the Appendix).

$$QTcF = a + b1 \cdot \text{conc} + b2 \cdot \text{BMI} + \varepsilon$$

The final model showed a significant effect of lapatinib concentration on QTcF. A significant effect of BMI was also seen. Prior medication use did not have a significant effect on the QTcF. [Note: if prior medication use was coded as a multinomial variable as done by the sponsor, the effect is still not significant.] Gender did not have a significant effect on the concentration-QTcF relationship.

BSV for slope was substantial while BSV for the intercept (baseline QTcF) was low. The following table (table 10a) shows the final model parameter estimates. Figure 4 shown below shows the concentration-QTcF relationship along with the predicted curve for a typical BMI (26.52 kg/m²).

Table 10a. Final model parameter estimates for linear mixed-effects analysis of QTcF data from study EGF10003.

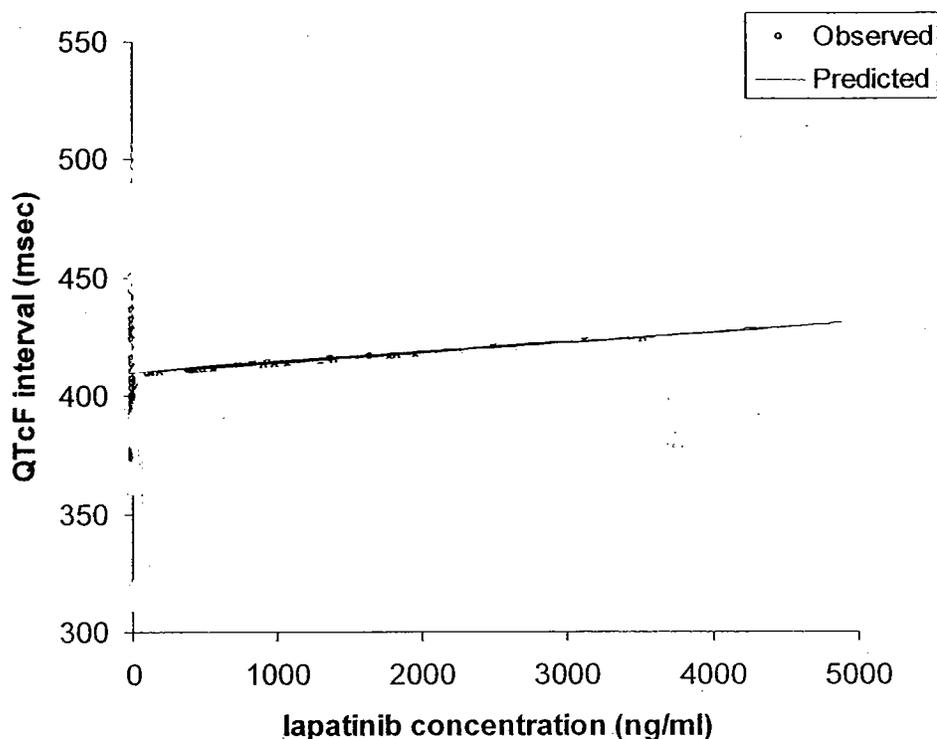
PARAMETER	Estimate
Intercept (mean± SE)	362.3 ± 19.4
Coefficient (b1) for Conc (mean± SE)	0.0042 ± 0.0019 (p=0.0355)
Coefficient (b2) for BMI (mean± SE)	1.803 ± 0.719 (p=0.0125)
BSV for Intercept (%CV)	5.8%
BSV for coefficient for Conc (%CV)	158%
Residual variability (msec)	18.2

The reviewer also evaluated a model using only lapatinib concentration as the predictor of QTcF. The results of this analysis are tabulated below in table 10b, and indicates that the relationship between QTcF and concentration remains significant with a slope of 0.0042, which is very similar to the estimate obtained with the “final model” that included both concentration and BMI.

Table 10b. Parameter estimates for model without BMI using linear mixed-effects analysis of QTcF data from study EGF10003.

PARAMETER	Estimate
Intercept (mean± SE)	410.03 ± 3.93
Coefficient (b1) for Conc (mean± SE)	0.0042 ± 0.0019 (p=0.0353)
BSV for Intercept (%CV)	5.6%
BSV for coefficient for conc (%CV)	161%
Residual variability (msec)	18.2

Figure 4: Lapatinib concentration vs. QTcF interval. Predicted curve is based on the final model and estimated for a typical BMI (26.52 kg/m²).



Based on the estimate and SE of the slope, the predicted change in QTcF can be predicted at various concentrations.

The following table 11 shows the predicted change in QTcF at mean concentrations following the 1200 mg daily dose in the current study (EGF10003) as well as at mean concentrations following the 1250 mg daily dose used in a different study of lapatinib in combination with capecitabine in advanced solid tumor patients (study EGF10005). This regimen is the same as the one recommended in the label, and is clinically relevant as lapatinib concentrations were increased by approximately 25-30% in presence of capecitabine in study EGF10005. Predicted changes in QTcF were also calculated using the upper 95% confidence limit of the slope.

Table 11: Predicted change in QTcF interval at various target peak concentrations.

Condition	Predicted change in QTcF interval (msec)	
	using slope	using upper 95% confidence limit of slope
study EGF10003 (single agent) Dose=1200 mg QD		
Mean Day 14 Cmax (1389 ng/ml)	5.8	10.2
study EGF10005 (combination with capecitabine) Dose=1250 mg QD		
Mean Cmax (3203 ng/ml)	13.5	23.4

As the table above indicates, at mean peak concentrations following the recommended lapatinib dose (in combination with capecitabine), the predicted QTc prolongation is 13.5 msec. Using the upper 95% confidence limit of the slope, the predicted QTc prolongation is predicted to be 23.4 msec.

Additionally, factors that could increase lapatinib concentrations, such as co-administration of CYP3A4 inhibitors (3.5-fold increase in AUC), administration of drug with food (3-4-fold increase in AUC), or administration to patients with hepatic impairment (56-85% increase in AUC), would be expected to further prolong the QTc interval.

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9.0. APPENDIX

Figure A1.1: DeltaQTcF vs. time on day 14 for each patient, by dose group.

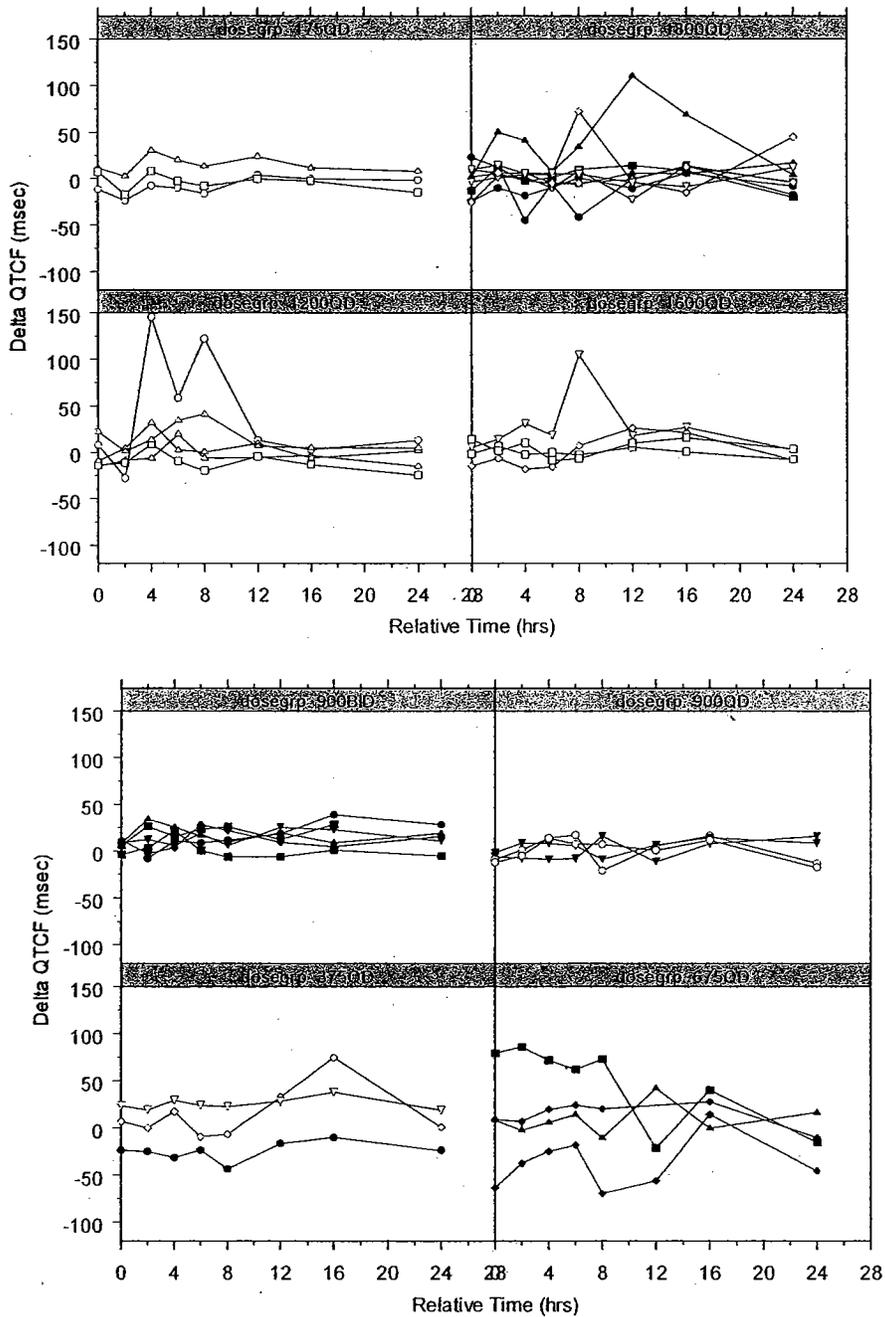
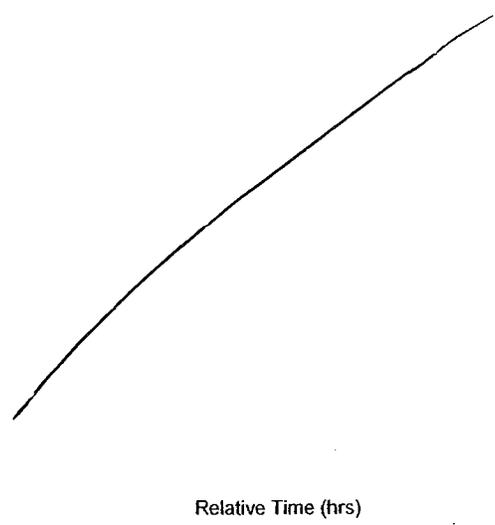
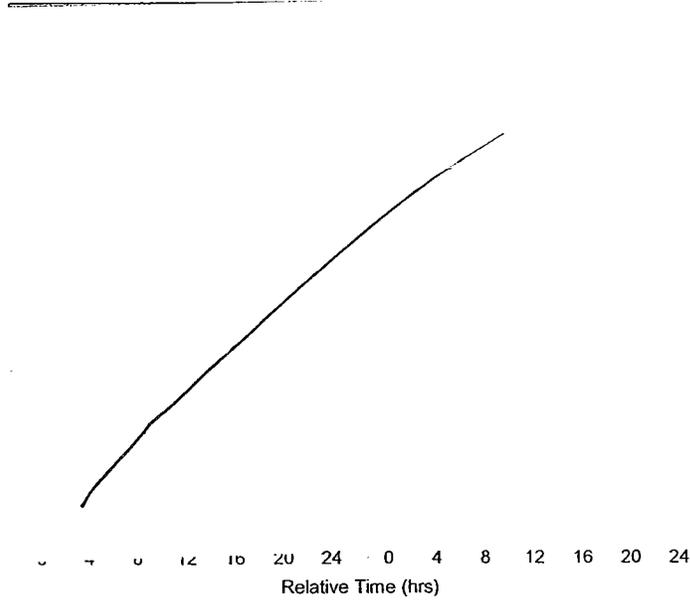


Figure A 1.2: Concentration vs. time on day 14 for each patient, by dose group.



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/s/

Christine Garnett
12/14/2006 04:17:52 PM
PHARMACOLOGIST

Shari Targum
12/15/2006 10:59:55 AM
MEDICAL OFFICER

Norman Stockbridge
12/15/2006 02:19:00 PM
MEDICAL OFFICER