Clinical trial results:
Effectiveness of first line treatment with lapatinib and ECF/X in histologically proven adenocarcinoma of the stomach or the esophagogastric junction (metastatic or not amenable to curative surgery) according to HER2 and EGFR status: a randomized phase II trial

Summary

EudraCT number	2009-011580-36
Trial protocol	BE DE HU PT
Global end of trial date	04 March 2014

Results information

Result version number	v1 (current)
This version publication date	13 August 2016
First version publication date	13 August 2016

Trial information

Trial identification

Sponsor protocol code	40071

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01123473
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	European Organisation for Research and Treatment of Cancer
Sponsor organisation address	Avenue E. Mounier 83/11, Brussels, Belgium, 1200
Public contact	Project, Budget and Regulatory Dept, European Organisation for Research and Treatment of Cancer, +32 27441062, regulatory@eortc.be
Scientific contact	Project, Budget and Regulatory Dept, European Organisation for Research and Treatment of Cancer, +32 27441062, regulatory@eortc.be

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 June 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 March 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To test the activity of lapatinib in patients HER2 positive by FISH and by IHC 2+ and 3+.

Protection of trial subjects:

The responsible investigator ensured that this study was conducted in agreement with either the Declaration of Helsinki (available on the World Medical Association web site (http://www.wma.net)) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient. The protocol had been written, and the study was conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online at http://www.ema.europa.eu/pdfs/human/ich/013595en.pdf). The protocol was approved by the competent ethics committee(s) as required by the applicable national legislation.

Background therapy:

Reference therapy consists of ECF (epirubicin, cisplatin, infusional 5-FU) or the alternative ECX (epirubicin, cisplatin, capecitabine). The choice of 5-FU versus capecitabine is provided on an institutional basis.
ECF/X (3-weekly cycles):
Epirubicin 50 mg/m2 D1
Cisplatin 60 mg/m2 D1
FU 200 mg/m2 D1-D21 in continuous infusion with a pump (Electronic or Baxter type) through a port-a-cath or Capecitabine 1250 mg/m2 fractionnated into two daily oral doses D1-D21

The duration of chemotherapy (ECX/ECF) is six cycles (18 weeks) unless terminated by patient refusal, death, progressive disease or toxicity.

Evidence for comparator:

ECF is the most widely accepted regime for gastric cancer, and the alternative ECX is considered equivalent (Ref. REAL2 study: Journal of Clinical Oncology, 2006 ASCO Annual Meeting Proceedings Part I. Vol 24, No. 18S (June 20 Supplement), 2006: LBA4017). The choice of 5-FU versus capecitabine is provided on an institutional basis because 1) capecitabine is not reimbursable in all countries, and 2) the trial should reflect present and future choices in order to have maximal impact on practice. Each center was free to choose between ECF and ECX before starting the trial. This choice had to be kept for all the subjects enrolled for the duration of the trial.

Actual start date of recruitment	16 February 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Portugal: 8
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Germany: 29
Country: Number of subjects enrolled	Hungary: 22

Worldwide total number of subjects	72
EEA total number of subjects	72

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	47
From 65 to 84 years	25
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between 16/02/2011 and 09/08/2013, patients with previously untreated adenocarcinoma of the stomach or the oesophagogastric junction that was metastatic or not amenable to curative surgery were recruited in 4 countries (Belgium, Germany, Hungary, Portugal). Patients were screened centrally for HER2 and EGFR status, both by FISH and IHC.

Pre-assignment

Screening details:

Eligibility criteria for HER2 and EGFR status (central testing):
-HER2 positive status by IHC or EGFR positive status by FISH or IHC
Protocol was amended on 03/02/2012 to exclude patients with HER2 FISH+ and IHC 2/3+ tumors.
-Negative HER2 status by FISH or negative HER2 status by IHC

Pre-assignment period milestones

Number of subjects started	72
Intermediate milestone: Number of subjects	Central testing for HER2 and EGFR status: 69
Number of subjects completed	29

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Tissue sample not delivered to central laboratory: 1
Reason: Number of subjects	Unknown: 1
Reason: Number of subjects	Consent withdrawn by subject: 5
Reason: Number of subjects	Physician decision: 1
Reason: Number of subjects	HER2+ by both IHC and FISH after amendment: 2
Reason: Number of subjects	Not eligible (HER2- and EGFR-): 30
Reason: Number of subjects	Not eligible (other reasons): 2
Reason: Number of subjects	Adverse event, non-fatal: 1

Period 1

Period 1 title	From randomization (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Knowledge of the treatment was concealed from the people who organize and analyze the data of a study as well as from subjects and investigators (CDISC Clinical Research Glossary Version 8.0). After progression, the treatment was unblinded to the investigator. Subjects receiving lapatinib were treated at the investigator discretion. Subjects in the control arm were offered lapatinib to be taken alone or in combination with chemotherapy such as ECF/ECX or FOLFOX up to further progression.

Arms

Are arms mutually exclusive?	Yes

Arm title	ECF/X + Lapatinib

Arm description:

ECF/X (3-weekly cycles) + Lapatinib.

The duration of chemotherapy (ECX/ECF) is six cycles (18 weeks) unless terminated by patient refusal, death, progressive disease or toxicity. Lapatinib was to be continued until refusal, death, progression or toxicity.

Arm type	Experimental
Investigational medicinal product name	Lapatinib
Investigational medicinal product code	GW572016
Other name	Tykerb
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Lapatinib: 1250mg/d po once daily continuously.
Lapatinib tablets (250 mg) are oval, biconvex, orange, film-coated tablets with one side of the tablet plain and other side of the tablet debossed with FG HLS. The tablets contain 405 mg of GW572016 Ditosylate Monohydrate, equivalent to 250 mg GW572016 free base per tablet. Oral lapatinib was supplied as 250 mg tablets packaged as 90 tablets per bottle.

Investigational medicinal product name	Epirubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Epirubicin 50 mg/m2 on day 1 (3-weekly cycles for 6 cycles)

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Cisplatin 60 mg/m2 on day 1 (3-weekly cycles for 6 cycles)

Investigational medicinal product name	5-FU
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

FU 200 mg/m2 from day 1 to day 21 (3-weekly cycles for 6 cycles) in continuous infusion with a pump (Electronic or Baxter type) through a port-a-cath.

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine 1250 mg/m2 fractionnated into two daily oral doses from day 1 to day 21 (3-weekly cycles for 6 cycles)

Arm title	ECF/X + Placebo

Arm description:

ECF/X (3-weekly cycles) + Placebo.

The duration of chemotherapy (ECX/ECF) is six cycles (18 weeks) unless terminated by patient refusal, death, progressive disease or toxicity. Placebo was to be continued until refusal, death, progression or

toxicity. After progression, treatment was unblinded and subjects in the control arm were offered lapatinib to be taken alone or in combination with chemotherapy such as ECF/ECX or FOLFOX up to further progression.

Arm type	Active comparator
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo: 1250mg/d po once daily continuously
Placebo tablets will be identical to active lapatinib oval, biconvex, orange, film-coated that are debossed on one side with FG HLS. The tablets contain microcrystallin cellulose and lactose. Placebo was supplied as 250 mg tablets packaged as 90 tablets per bottle.

Investigational medicinal product name	Epirubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Epirubicin 50 mg/m2 on day 1 (3-weekly cycles for 6 cycles)

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Cisplatin 60 mg/m2 on day 1 (3-weekly cycles for 6 cycles)

Investigational medicinal product name	5-FU
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

FU 200 mg/m2 from day 1 to day 21 (3-weekly cycles for 6 cycles) in continuous infusion with a pump (Electronic or Baxter type) through a port-a-cath

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine 1250 mg/m2 fractionnated into two daily oral doses from day 1 to day 21 (3-weekly cycles for 6 cycles)

Number of subjects in period 1[1]	ECF/X + Lapatinib	ECF/X + Placebo
Started	15	14
Completed	10	10
Not completed	5	4
Physician decision	3	1
Consent withdrawn by subject	1	-
Adverse event, non-fatal	1	3

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 72 patients were registered and 29 patients were tested for their HER2 and EGFR status by the central laboratory. Patients without any tumor HER2 or EGFR overexpression or amplification were to be excluded per protocol. Protocol was amended on 03/02/2012 to further exclude patients with HER2 FISH+ and IHC 2/3+ tumors. A total of 29 patients were randomized.

Baseline characteristics

Reporting groups	
Reporting group title	ECF/X + Lapatinib
Reporting group description:	
ECF/X (3-weekly cycles) + Lapatinib. The duration of chemotherapy (ECX/ECF) is six cycles (18 weeks) unless terminated by patient refusal, death, progressive disease or toxicity. Lapatinib was to be continued until refusal, death, progression or toxicity.	
Reporting group title	ECF/X + Placebo
Reporting group description:	
ECF/X (3-weekly cycles) + Placebo. The duration of chemotherapy (ECX/ECF) is six cycles (18 weeks) unless terminated by patient refusal, death, progressive disease or toxicity. Placebo was to be continued until refusal, death, progression or toxicity. After progression, treatment was unblinded and subjects in the control arm were offered lapatinib to be taken alone or in combination with chemotherapy such as ECF/ECX or FOLFOX up to further progression.	

Reporting group values	ECF/X + Lapatinib	ECF/X + Placebo	Total
Number of subjects	15	14	29
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	5	10	15
From 65-84 years	10	4	14
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	2	4	6
Male	13	10	23
HER2 and EGFR status			
Result of the central testing for HER2 and EGFR status by fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC).			
Units: Subjects			
HER2 FISH+ and IHC 2/3+	4	2	6
HER2 FISH- and IHC 2/3+	2	3	5
HER2 IHC 0/1+ and EGFR FISH+ or IHC 2/3+	9	9	18
Histological grade Units: Subjects			
GI	2	0	2
GII	5	7	12
GIII	4	3	7
Unknown	4	4	8

Site of the tumor Units: Subjects			
Stomach	11	5	16
Esophagogastric junction	3	5	8
Both	1	4	5
T-stage Units: Subjects			
cT1	0	1	1
cT3	4	2	6
cT4	0	3	3
cTX	10	8	18
Unknown	1	0	1
N-stage Units: Subjects			
cN0	1	0	1
cN1	3	2	5
cN2	2	3	5
cN3	2	2	4
cNX	6	7	13
Unknown	1	0	1
M-stage Units: Subjects			
cM0	1	0	1
cM1	14	14	28

Subject analysis sets

Subject analysis set title	Patients HER2- by IHC and EGFR+ in ECF/X + Lapatinib
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients HER2 IHC 0/1+ and EGFR FISH+ or IHC 2/3+ (EGFR+) in the ECF/X + Lapatinib Arm	
Subject analysis set title	Patients HER2- by IHC and EGFR+ in ECF/X + Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients HER2 IHC 0/1+ and EGFR FISH+ or IHC 2/3+ (EGFR+) in the ECF/X + Placebo Arm	

Reporting group values	Patients HER2- by IHC and EGFR+ in ECF/X + Lapatinib	Patients HER2- by IHC and EGFR+ in ECF/X + Placebo	
Number of subjects	9	9	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	1	6	
From 65-84 years	8	3	
85 years and over	0	0	

Gender categorical Units: Subjects			
Female	1	2	
Male	8	7	
HER2 and EGFR status			
Result of the central testing for HER2 and EGFR status by fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC).			
Units: Subjects			
HER2 FISH+ and IHC 2/3+	0	0	
HER2 FISH- and IHC 2/3+	0	0	
HER2 IHC 0/1+ and EGFR FISH+ or IHC 2/3+	9	9	
Histological grade Units: Subjects			
GI	2	0	
GII	4	4	
GIII	1	2	
Unknown	2	3	
Site of the tumor Units: Subjects			
Stomach	7	4	
Esophagogastric junction	1	3	
Both	1	2	
T-stage Units: Subjects			
cT1	0	1	
cT3	3	0	
cT4	0	2	
cTX	5	6	
Unknown	1	0	
N-stage Units: Subjects			
cN0	0	0	
cN1	2	1	
cN2	1	3	
cN3	1	0	
cNX	4	5	
Unknown	1	0	
M-stage Units: Subjects			
cM0	0	0	
cM1	9	9	

End points

End points reporting groups

Reporting group title	ECF/X + Lapatinib

Reporting group description:

ECF/X (3-weekly cycles) + Lapatinib.

The duration of chemotherapy (ECX/ECF) is six cycles (18 weeks) unless terminated by patient refusal, death, progressive disease or toxicity. Lapatinib was to be continued until refusal, death, progression or toxicity.

Reporting group title	ECF/X + Placebo

Reporting group description:

ECF/X (3-weekly cycles) + Placebo.

The duration of chemotherapy (ECX/ECF) is six cycles (18 weeks) unless terminated by patient refusal, death, progressive disease or toxicity. Placebo was to be continued until refusal, death, progression or toxicity. After progression, treatment was unblinded and subjects in the control arm were offered lapatinib to be taken alone or in combination with chemotherapy such as ECF/ECX or FOLFOX up to further progression.

Subject analysis set title	Patients HER2- by IHC and EGFR+ in ECF/X + Lapatinib
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients HER2 IHC 0/1+ and EGFR FISH+ or IHC 2/3+ (EGFR+) in the ECF/X + Lapatinib Arm

Subject analysis set title	Patients HER2- by IHC and EGFR+ in ECF/X + Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients HER2 IHC 0/1+ and EGFR FISH+ or IHC 2/3+ (EGFR+) in the ECF/X + Placebo Arm

Primary: Progression-Free Survival

End point title	Progression-Free Survival

End point description:

Progression Free Survival was computed from the date of randomization to the date of first progression according to the RECIST criteria (version 1.1) or death, whatever comes first. Patients alive and free of progression prior to the analysis cut-off date are censored at the date of the most recent assessment.

End point type	Primary

End point timeframe:

Tumor evaluation after start of treatment, CT scans or MRI were performed every 8 weeks during treatment. Patients who stopped treatment without progression were followed-up for progression every 3 months during the first 2 years and then every 6 months.

End point values	ECF/X + Lapatinib	ECF/X + Placebo	Patients HER2- by IHC and EGFR+ in ECF/X + Lapatinib	Patients HER2- by IHC and EGFR+ in ECF/X + Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	14[1]	14	9	9
Units: Months				
median (confidence interval 95%)	7.95 (4.24 to 11.27)	5.88 (4.14 to 9.92)	7.95 (1.41 to 13.83)	6.32 (1.84 to 12.19)

Notes:

[1] - 1 patient not eligible (no evidence of metastases and amenable to surgery) was excluded.

Statistical analyses

Statistical analysis title	Primary analysis (per protocol population)

Statistical analysis description:

Enrollment was curtailed after announcement of the LOGIC trial results (ASCO 2013). Therefore the original decision rule could not be applied. No formal statistical tests were carried out due to the low number of patients accrued. Efficacy analyses were done on the per protocol population (all patients eligible who started their allocated treatment). PFS curve was estimated using the Kaplan-Meier technique by treatment arm. Median PFS is reported with its 95% confidence interval.

Comparison groups	ECF/X + Lapatinib v ECF/X + Placebo
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	1.99

Notes:

[2] - Due to the low number of patients accrued, only descriptive statistics are provided.

Statistical analysis title	Subgroup analysis (HER2- by IHC and EGFR+)

Statistical analysis description:

The primary subgroup of interest in this trial was the population of patients HER2 by IHC 0/1+ / EGFR+ by FISH or EGFR+ by IHC 2/3+. PFS was estimated using the Kaplan-Meier technique by treatment arm in this subgroup. Median PFS is reported with its 95% confidence interval in this subgroup.

Comparison groups	Patients HER2- by IHC and EGFR+ in ECF/X + Lapatinib v Patients HER2- by IHC and EGFR+ in ECF/X + Placebo
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	2.46

Notes:

[3] - Due to the low number of patients accrued, only descriptive statistics are provided.

Secondary: Progression Free Survival (Sensitivity)

End point title	Progression Free Survival (Sensitivity)

End point description:

Progression Free Survival was computed from the date of randomization to the date of first progression counting clinical progressions/symptomatic deteriorations as events for PFS or death, whatever comes first. Patients alive and free of progression (clinical PD or PD according to RECIST v. 1.1) prior to the analysis cut-off date were censored at the date of the most recent assessment.

End point type	Secondary

End point timeframe:

Tumor evaluation after start of treatment, CT scans or MRI were performed every 8 weeks during treatment. Patients who stopped treatment without progression were followed-up for progression every 3 months during the first 2 years and then every 6 months.

End point values	ECF/X + Lapatinib	ECF/X + Placebo	Patients HER2- by IHC and EGFR+ in ECF/X + Lapatinib	Patients HER2- by IHC and EGFR+ in ECF/X + Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	14[4]	14	9	9
Units: Months				
median (confidence interval 95%)	7.1 (2.33 to 11.27)	5.88 (4.14 to 9.92)	6.21 (1.38 to 13.83)	6.32 (1.84 to 12.19)

Notes:

[4] - 1 patient not eligible (no evidence of metastases and amenable to surgery) was excluded.

Statistical analyses

Statistical analysis title	Sensitivity analysis

Statistical analysis description:

The primary analysis on PFS was redone counting clinical progressions/symptomatic deteriorations as additional events for PFS and censoring patients alive and free of progression (clinical PD or PD according to RECIST v. 1.1) prior to the analysis cut-off date at the date of the most recent assessment.

Comparison groups	ECF/X + Lapatinib v ECF/X + Placebo
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[5]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	2.14

Notes:

[5] - Sensitivity analysis

Statistical analysis title	Subgroup analysis (HER2- by IHC and EGFR+)

Statistical analysis description:

The subgroup analysis of PFS in patients HER2 by IHC 0/1+ / EGFR+ by FISH or EGFR+ by IHC 2/3+ was redone counting clinical progressions/symptomatic deteriorations as additional events for PFS and censoring patients alive and free of progression (clinical PD or PD according to RECIST v. 1.1) prior to the analysis cut-off date at the date of the most recent assessment.

Comparison groups	Patients HER2- by IHC and EGFR+ in ECF/X + Placebo v Patients HER2- by IHC and EGFR+ in ECF/X + Lapatinib
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other[6]
Parameter estimate	Log hazard ratio
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	2.75

Notes:

[6] - Sensitivity analysis in the primary subgroup of interest

Secondary: Best overall response

End point title	Best overall response

End point description:

Objective tumor response was measured according to the RECIST criteria version 1.1. All patients had their BEST RESPONSE from the start of study treatment until the end of treatment classified as: complete Response (CR), partial Response (PR), stable Disease (SD), progressive Disease (PD), early death or not evaluable.

End point type	Secondary

End point timeframe:

Tumor evaluation after start of treatment, CT scans or MRI were performed every 8 weeks during treatment. Best overall response was assessed from the start of study treatment until the end of treatment.

End point values	ECF/X + Lapatinib	ECF/X + Placebo	Patients HER2- by IHC and EGFR+ in ECF/X + Lapatinib	Patients HER2- by IHC and EGFR+ in ECF/X + Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	14[7]	14	9	9
Units: Patient				
CR	0	0	0	0
PR	6	3	4	2
SD	5	6	2	3
PD	2	3	2	2
Early death from malignant disease	1	0	1	0
Not evaluable	0	2	0	2

Notes:

[7] - 1 patient not eligible (no evidence of metastases and amenable to surgery) was excluded.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall survival was computed from the date of randomization to the date of death. Patients still alive at the analysis cut-off date were censored at the date of the most recent follow-up.

End point type	Secondary

End point timeframe:

After end of treatment, patients were followed-up for survival every 3 months during the first 2 years and then every 6 months thereafter.

End point values	ECF/X + Lapatinib	ECF/X + Placebo	Patients HER2-by IHC and EGFR+ in ECF/X + Lapatinib	Patients HER2-by IHC and EGFR+ in ECF/X + Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	14[8]	14	9	9
Units: Months				
median (confidence interval 95%)	13.83 (5.45 to 22.54)	10.09 (4.37 to 22.54)	9.92 (1.41 to 13.83)	9.26 (2.33 to 20.73)

Notes:

[8] - 1 patient not eligible (no evidence of metastases and amenable to surgery) was excluded.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were collected at baseline before starting treatment, at the end of each cycle during treatment and 8 weeks after last administration of treatment. In case of treatment-related toxicity, follow-up was until resolution of the AE.

Adverse event reporting additional description:

CRF for AEs contains pre-specified items + additional boxes for all "other" AEs. AEs are evaluated using CTC grading, SAEs using MedDra. Non-SAEs has not been collected specifically, therefore all AEs will be reported in non-SAE section.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	ECF/X + Placebo

Reporting group description:

Safety population: randomized patients who started placebo

Reporting group title	ECF/X + Lapatinib

Reporting group description:

Safety population: randomized patients who started lapatinib

Serious adverse events	ECF/X + Placebo	ECF/X + Lapatinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 14 (42.86%)	8 / 15 (53.33%)	
number of deaths (all causes)	9	9	
number of deaths resulting from adverse events	0	0	
Investigations			
Urine output decreased	Additional description: From pharmacovigilance database.		
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis	Additional description: From pharmacovigilance database.		
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Coronary artery disease	Additional description: From pharmacovigilance database.		
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness	Additional description: From pharmacovigilance database.		
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure	Additional description: From pharmacovigilance database.		
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Leukopenia	Additional description: From pharmacovigilance database.		
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia	Additional description: From pharmacovigilance database.		
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 14 (7.14%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Disease progression	Additional description: From pharmacovigilance database.		
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue	Additional description: From pharmacovigilance database.		

alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration	Additional description: From pharmacovigilance database.		
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 14 (14.29%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Gastrointestinal disorders			
Abdominal pain	Additional description: From pharmacovigilance database.		
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites	Additional description: From pharmacovigilance database.		
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea	Additional description: From pharmacovigilance database.		
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 14 (7.14%)	2 / 15 (13.33%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic	Additional description: From pharmacovigilance database.		
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea	Additional description: From pharmacovigilance database.		
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting	Additional description: From pharmacovigilance database.		
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 14 (7.14%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hyperbilirubinaemia	Additional description: From pharmacovigilance database.		
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	Additional description: From pharmacovigilance database.		
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 14 (0.00%)	2 / 15 (13.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pleural effusion	Additional description: From pharmacovigilance database.		
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia	Additional description: From pharmacovigilance database.		
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis	Additional description: From pharmacovigilance database.		
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia	Additional description: From pharmacovigilance database.		
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	ECF/X + Placebo	ECF/X + Lapatinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 14 (100.00%)	15 / 15 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Other NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Phlebitis	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Flushing	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Thromboembolic event	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	

General disorders and administration site conditions			
Fatique	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	13 / 14 (92.86%)	11 / 15 (73.33%)	
occurrences (all)	13	11	
Fever	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 14 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	2	1	
Other GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	6 / 14 (42.86%)	5 / 15 (33.33%)	
occurrences (all)	6	5	
Immune system disorders			
Allergic reaction	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Other REPRODUCTIVE SYSTEM AND BREAST DISORDERS	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Dyspnea	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 14 (21.43%)	4 / 15 (26.67%)	
occurrences (all)	3	4	
Cough	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 14 (14.29%)	2 / 15 (13.33%)	
occurrences (all)	2	2	

Other RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	4 / 14 (28.57%)	3 / 15 (20.00%)	
occurrences (all)	4	3	
Pleural effusion	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Psychiatric disorders			
Other PSYCHIATRIC DISORDERS	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 14 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	2	1	
Investigations			
Other INVESTIGATIONS	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	4 / 14 (28.57%)	3 / 15 (20.00%)	
occurrences (all)	4	3	
Cardiac disorders			
Other CARDIAC DISORDERS	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 14 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	2	1	
Sinus bradycardia	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 14 (7.14%)	3 / 15 (20.00%)	
occurrences (all)	1	3	
Other NERVOUS SYSTEM DISORDERS	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE			

4.0			
subjects affected / exposed	7 / 14 (50.00%)	4 / 15 (26.67%)	
occurrences (all)	7	4	
Peripheral sensory neuropathy	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	4 / 14 (28.57%)	3 / 15 (20.00%)	
occurrences (all)	4	3	
Blood and lymphatic system disorders			
Febrile neutropenia	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 14 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Ear and labyrinth disorders			
Hearing impaired	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 14 (7.14%)	2 / 15 (13.33%)	
occurrences (all)	1	2	
Eye disorders			
Other EYE DISORDERS	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Costipation	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	5 / 14 (35.71%)	2 / 15 (13.33%)	
occurrences (all)	5	2	
Diarrhea	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	6 / 14 (42.86%)	12 / 15 (80.00%)	
occurrences (all)	6	12	
Mucositis oral	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	2 / 14 (14.29%)	4 / 15 (26.67%)	
occurrences (all)	2	4	
Nausea	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	11 / 14 (78.57%)	9 / 15 (60.00%)	
occurrences (all)	11	9	
Other GASTROINTESTINAL DISORDERS	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	10 / 14 (71.43%)	8 / 15 (53.33%)	
occurrences (all)	10	8	
Vomiting	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	5 / 14 (35.71%)	10 / 15 (66.67%)	
occurrences (all)	5	10	
Skin and subcutaneous tissue disorders			
Alopecia	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 14 (21.43%)	4 / 15 (26.67%)	
occurrences (all)	3	4	
Dry skin	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 14 (21.43%)	5 / 15 (33.33%)	
occurrences (all)	3	5	
Other SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 14 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	2	1	
Palma-plantar erythrodysesthesia syndrome	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	5 / 14 (35.71%)	5 / 15 (33.33%)	
occurrences (all)	5	5	
Rash maculo-papular	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		

alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Pruritus	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Other RENAL AND URINARY DISORDERS	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Other MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 14 (21.43%)	3 / 15 (20.00%)	
occurrences (all)	3	3	
Infections and infestations			
Other INFECTIONS AND INFESTATIONS	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 14 (7.14%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Papulopustular rash	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 14 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Paronychia	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 14 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
Anorexia	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	4 / 14 (28.57%)	6 / 15 (40.00%)	
occurrences (all)	4	6	
Other METABOLISM AND NUTRITION DISORDERS	Additional description: From clinical database. All clinical adverse events (any grade) during treatment.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 September 2012	Global Amendment number 1 (the only one): Modifications to the current protocol from version v2.0 dated 20JUL2010 to version 3.0 dated 03FEB2012. Description of the amendment: The main changes affecting the primary objective of the study&change in the patient eligibility criteria: The targeted patient populations for this study has been amended taking into account the indication for Herceptin. Initially, the trial was designed to assess in a randomized fashion the potential efficacy of lapatinib in both EGFR+/HER-2 and HER 2+ gastric tumors (weakly and strongly HER-2+) measured by IHC and FISH. Based on the indication of herceptin for HER-2+ patients, the strongly-positive HER-2 group (HER2+ by FISH/ HER2+ by IHC 2/3+) has been excluded from study entry. Accordingly, the eligibility criteria for the patient population have been amended and the randomization PIS/IC for the subject have been modified to reflect these changes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported