Clinical trial results:
An Open-label, Multi-center Study to Evaluate the Disease Free Survival Rate of a Perioperative Combination of Capecitabine (Xeloda), Trastuzumab (Herceptin) and Oxaliplatin (XELOX-Trastuzumab) in Patients With Resectable Gastric or Gastro-esophageal Junction Adenocarcinoma (stages II-IV).

Summary

EudraCT number	2009-017848-14
Trial protocol	ES
Global end of trial date	10 June 2014

Results information

Result version number	v1 (current)
This version publication date	06 April 2016
First version publication date	06 April 2016

Trial information

Trial identification

Sponsor protocol code	ML25189

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01130337
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, CH-4070, Basel, Switzerland,
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com

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	10 June 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 June 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was a Phase II, open-label, non-comparative, national, multicenter study with competitive recruitment to investigate the perioperative administration of one of the regimens considered to be standard in the treatment of Gastric Cancer (GC) in combination with trastuzumab.

Protection of trial subjects:

Participants willing to participate were informed of the nature of the trial in detail and thereafter signed the informed consent form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 July 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	25 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 36
Worldwide total number of subjects	36
EEA total number of subjects	36

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)	16
From 65 to 84 years	19

85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening period comprised of 35 days. A total of 136 participants were included in the study out of which 36 participants were enrolled and 100 participants discontinued due to screening failures. Abbreviation of AE= adverse event.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Capecitabine+Oxaliplatin+Trastuzumab

Arm description:

Participants received 3 cycles of capecitabine (1,000 milligrams per meter squared [mg/m^2] tablet orally [p.o] twice daily, Days 1-14)/oxaliplatin (130 mg/m^2 as a 120-minute intravenous [IV] infusion, Day 1 of the cycle)/trastuzumab (8 milligrams per kilograms [mg/kg] on Day 1, followed by doses of 6 mg/kg as IV infusion) (XELOX-trastuzumab) as neoadjuvant treatment, every 3 weeks, thereafter, they were assessed for surgery. After surgery, participants received 3 cycles of XELOX-trastuzumab as treatment adjuvant to the surgery, thereafter, another 12 cycles of trastuzumab as monotherapy, was administered every 3 weeks, until disease progression or death.

Arm type	Experimental
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	Xeloda
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received capecitabine 1,000 mg/m^2 tablet p.o twice daily, Days 1-14, every 3 weeks.

Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received oxaliplatin 130 mg/m^2 as a 120-minute IV infusion Day 1 of the cycle, every 3 weeks.

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received trastuzumab 8 mg/kg on Day 1, followed by doses of 6 mg/kg as IV infusion, every 3 weeks.

Number of subjects in period 1	Capecitabine+Oxaliplatin+Trastuzumab
Started	36
Completed	22
Not completed	14
Consent withdrawn by subject	3
Disease progression	1
Death	1
Principal investigator decision	1
Toxicity, AE/intercurrent disease	7
Surgical resection (R2)	1

Baseline characteristics

Reporting groups	
Reporting group title	Capecitabine+Oxaliplatin+Trastuzumab

Reporting group description:

Participants received 3 cycles of capecitabine (1,000 milligrams per meter squared [mg/m^2] tablet orally [p.o] twice daily, Days 1-14)/oxaliplatin (130 mg/m^2 as a 120-minute intravenous [IV] infusion, Day 1 of the cycle)/trastuzumab (8 milligrams per kilograms [mg/kg] on Day 1, followed by doses of 6 mg/kg as IV infusion) (XELOX-trastuzumab) as neoadjuvant treatment, every 3 weeks, thereafter, they were assessed for surgery. After surgery, participants received 3 cycles of XELOX-trastuzumab as treatment adjuvant to the surgery, thereafter, another 12 cycles of trastuzumab as monotherapy, was administered every 3 weeks, until disease progression or death.

Reporting group values	Capecitabine+Oxaliplatin+Trastuzumab	Total	
Number of subjects	36	36	
Age categorical Units: Subjects			

Age Continuous Units: years			
arithmetic mean	63.44		
standard deviation	± 10.42	-	
Gender, Male/Female Units: participants			
Female	7	7	
Male	29	29	

End points

End points reporting groups

Reporting group title	Capecitabine+Oxaliplatin+Trastuzumab

Reporting group description:

Participants received 3 cycles of capecitabine (1,000 milligrams per meter squared [mg/m^2] tablet orally [p.o] twice daily, Days 1-14)/oxaliplatin (130 mg/m^2 as a 120-minute intravenous [IV] infusion, Day 1 of the cycle)/trastuzumab (8 milligrams per kilograms [mg/kg] on Day 1, followed by doses of 6 mg/kg as IV infusion) (XELOX-trastuzumab) as neoadjuvant treatment, every 3 weeks, thereafter, they were assessed for surgery. After surgery, participants received 3 cycles of XELOX-trastuzumab as treatment adjuvant to the surgery, thereafter, another 12 cycles of trastuzumab as monotherapy, was administered every 3 weeks, until disease progression or death.

Primary: Percentage of Participants With Disease-free Survival (DFS) at Month 18

End point title	Percentage of Participants With Disease-free Survival (DFS) at Month 18[1]

End point description:

DFS was the time elapsed from the time of surgery (for complete resection [R0] participants) until the date on which progression or death from any cause was documented (whichever occurred first). Progression was defined as target lesions greater than (>) 20 percent (%) increase in the sum of the longest diameter (SLD) taking as reference the smallest SLD recorded since the treatment started (nadir) and minimum 5 millimeter (mm) increase over the nadir. When the sum becomes very small, increases within the measurement error (2-3 mm) can lead to a 20% increase. Participants who did not present progression and who had not died were censored on the last date on which it was known that there was no progression (last response assessment). Intent-to-treat (ITT) population included all enrolled participants.

End point type	Primary

End point timeframe:

Month 18

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the study was non-comparative in nature, no statistical analysis was performed.

End point values	Capecitabine+Oxaliplatin+Trastuzumab			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: percentage of participants				
number (confidence interval 95%)	76.12 (57.72 to 87.32)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Complete Tumor Resection (R0)

End point title	Percentage of Participants With Complete Tumor Resection (R0)

End point description:

R0 resection was defined as having performed a complete resection of the tumor with adequate tumor-free margins and regional lymph node extirpation. ITT population. Here "number of participants analyzed" included those who underwent surgery.

End point type	Secondary

End point timeframe:

Between Days 7 and 21 of the 3rd cycle of neoadjuvant treatment, thereafter, every 9 weeks during adjuvant treatment and then after adjuvant treatment every 3 months until Month 25

End point values	Capecitabine+ Oxaliplatin+Trastuzumab			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: percentage of participants				
number (confidence interval 95%)	90.32 (74.25 to 97.96)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Pathological Complete Response (pCR)

End point title	Percentage of Participants With Pathological Complete Response (pCR)

End point description:

pCR was defined as an absence of any invasive cancer cell of the primary tumor after the time of major neoadjuvant chemotherapy, with or without surgery. ITT population.

End point type	Secondary

End point timeframe:

Between Days 7 and 21 of the 3rd cycle of neoadjuvant treatment, thereafter, every 9 weeks during adjuvant treatment and then after adjuvant treatment every 3 months until Month 25

End point values	Capecitabine+ Oxaliplatin+Trastuzumab			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: percentage of participants				
number (confidence interval 95%)	8.33 (1.75 to 22.47)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Objective Response

End point title	Percentage of Participants With Objective Response

End point description:

An objective response was defined as either a complete response (CR) or a partial response (PR). Using the Response Evaluation Criteria in Solid Tumors (RECIST), CR was defined as the disappearance of all target lesions and all non-target lesions, normalization of tumor marker level, and no new lesions. PR was defined as the disappearance of all target lesions and persistence of greater than or equal to (≥) 1 non-target lesions and/or the maintenance of tumor marker level above the normal limits, or, at least a 30% decrease in the sum of the longest diameter of target lesions, and no new lesions or unequivocal progression of existing non-target lesions. ITT population.

End point type	Secondary

End point timeframe:

Between Days 7 and 21 of the 3rd cycle of neoadjuvant treatment, thereafter, every 9 weeks during adjuvant treatment and then after adjuvant treatment every 3 months until Month 25

End point values	Capecitabine+ Oxaliplatin+Trastuzumab			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: percentage of participants				
number (not applicable)	38.89			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Before Day 1 of each cycle until Month 25

Adverse event reporting additional description:

The safety analysis included all participants in the ITT population who received at least 1 dose of the study drugs.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Capecitabine+Oxaliplatin+Trastuzumab

Reporting group description:

Participants received 3 cycles of capecitabine (1,000 mg/m^2 tablet p.o twice daily, Days 1-14)/oxaliplatin (130 mg/m^2 as a 120-minute IV infusion Day 1 of the cycle)/trastuzumab (8 mg/kg on Day 1, followed by doses of 6 mg/kg as IV infusion) (XELOX-trastuzumab) as neoadjuvant treatment, every 3 weeks, thereafter, they were assessed for surgery. After surgery, participants received 3 cycles of XELOX-trastuzumab as treatment adjuvant to the surgery, thereafter, another 12 cycles of trastuzumab as monotherapy, was administered every 3 weeks, until disease progression or death.

Serious adverse events	Capecitabine+Oxaliplatin+Trastuzumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 36 (61.11%)		
number of deaths (all causes)	8		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Procedural complication			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anastomotic leak			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Peripheral ischaemia			

subjects affected / exposed	1 / 36 (2.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypovolaemic shock				
subjects affected / exposed	1 / 36 (2.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Cardiogenic shock				
subjects affected / exposed	1 / 36 (2.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Nervous system disorders				
Encephalopathy				
subjects affected / exposed	1 / 36 (2.78%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Mucosal inflammation				
subjects affected / exposed	1 / 36 (2.78%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Multi-organ failure				
subjects affected / exposed	1 / 36 (2.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pyrexia				
subjects affected / exposed	1 / 36 (2.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sudden death				
subjects affected / exposed	1 / 36 (2.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			

Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 36 (13.89%)		
occurrences causally related to treatment / all	6 / 6		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal ischaemia			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Dysphagia			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophageal perforation			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Localised intra-abdominal fluid collection			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			

subjects affected / exposed	2 / 36 (5.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Schizoaffective disorder			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Postoperative wound infection			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		

Abdominal sepsis			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Septic shock			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Capecitabine+Oxaliplatin+Trastuzumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 36 (97.22%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	5		
Ejection fraction decreased			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	4		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	6 / 36 (16.67%)		
occurrences (all)	11		
Neurotoxicity			
subjects affected / exposed	10 / 36 (27.78%)		
occurrences (all)	16		
Dysaesthesia			

subjects affected / exposed occurrences (all) Dysgeusia subjects affected / exposed occurrences (all) Neuropathy peripheral subjects affected / exposed occurrences (all) Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	7 / 36 (19.44%) 18 3 / 36 (8.33%) 5 6 / 36 (16.67%) 9 2 / 36 (5.56%) 6		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all)	 11 / 36 (30.56%) 13 4 / 36 (11.11%) 16 7 / 36 (19.44%) 16		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all) Mucosal inflammation subjects affected / exposed occurrences (all) Asthenia subjects affected / exposed occurrences (all)	 10 / 36 (27.78%) 13 8 / 36 (22.22%) 9 24 / 36 (66.67%) 61		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Constipation	 29 / 36 (80.56%) 68		

subjects affected / exposed	6 / 36 (16.67%)		
occurrences (all)	6		
Abdominal pain upper			
subjects affected / exposed	5 / 36 (13.89%)		
occurrences (all)	8		
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Abdominal pain			
subjects affected / exposed	9 / 36 (25.00%)		
occurrences (all)	12		
Dyspepsia			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	3		
Nausea			
subjects affected / exposed	17 / 36 (47.22%)		
occurrences (all)	29		
Dysphagia			
subjects affected / exposed	5 / 36 (13.89%)		
occurrences (all)	13		
Vomiting			
subjects affected / exposed	15 / 36 (41.67%)		
occurrences (all)	26		
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	13		
Dyspnoea			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	4		
Catarrh			

subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	7		
Rhinorrhoea			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Pruritus			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Nail disorder			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	4		
Rash			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	4		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	5		
Pain in extremity			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Muscle spasms			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Metabolism and nutrition disorders			

Decreased appetite subjects affected / exposed occurrences (all)	15 / 36 (41.67%) 30		
Hypokalaemia subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported