Clinical trial results:
A study of lapatinib in combination with oxaliplatin and capecitabine in early HER-2 overexpressing oesophageal and gastric cancers.

Summary

EudraCT number	2010-019602-16
Trial protocol	GB
Global end of trial date	26 March 2015

Results information

Result version number	v1 (current)
This version publication date	08 July 2016
First version publication date	30 July 2015

Trial information

Trial identification

Sponsor protocol code	N/A

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Cambridge University Hospitals NHS Foundation Trust
Sponsor organisation address	Hills Road, Cambridge University Hospitals NHS Foundation Trus, United Kingdom, CB2 0QQ
Public contact	Prasanna Kapilan, Cambridge clinical trials unit (CCTU) , +44 1223 216524, Prasanna.kapilan@addenbrookes.nhs.uk
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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	14 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 September 2014
Global end of trial reached?	Yes
Global end of trial date	26 March 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

"Assess ability of ex vivo molecular response to predict molecular response on a biopsy after 10 days of treatment with lapatinib, and to report observations of patterns of radiological, functional imaging and pathological response associated with molecular response"

Protection of trial subjects:

"Additional visits for investigations no risks. Where possible tests will be scheduled on the same day to minimise inconvenience.
Additional endoscopy: Minimal risk. Where possible pretreatment research biopsies will be obtained at a routine endoscopy visit rather than at an additional visit. The day 10 endoscopy is unavoidable.
Radiation risk from additional PET/CT scan: There is a small additional risk of second malignancy from the PET/CT scan and from MUGA scan if required. This is unavoidable but patients will be fully informed in the information sheet
Toxicity from Lapatinib: The main potential side effects from lapatinib are diarrhoea, skin rash and heart toxicity.
Diarrhoea and rash are normally easily managed without great distress to the patient. Heart toxicity is rare, but to
minimise the chance of it being a problem we will be monitoring heart function throughtout treatment with
echocardiograms. Although these tests involve an additional hospital visit they are noninvasive
and should not cause any discomfort or distress. In addition we have modified the standard chemotherapy to minimise the risk of toxicity of the combination of lapatinib with standard treatment. This involves omitting one drug (epirubicin) which is known to also damage heart tissue, and reducing the dose of capecitabine.
This combination at these doses has already been tested in gastric cancer and has been found to be safe and
effective, but to ensure patient safety we are performing a formal safety analysis after 6 patients have been recruited to ensure there is no need for further modifications."

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 May 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	United Kingdom: 10
Worldwide total number of subjects	10
EEA total number of subjects	10

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)	6
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

1st patient registered 05/07/2011, last patient registered 15/04/2013. Patients were recruited from two English sites in the patients' oncology clinics.

Pre-assignment

Screening details:

Patients underwent pre-treatment Oesophago-gastro-duodenoscopy (OGD) and biopsy.

Pre-assignment period milestones

Number of subjects started	187[1]
Number of subjects completed	10

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 9
Reason: Number of subjects	Not meeting inclusion criteria as HER2 negative: 134
Reason: Number of subjects	Not meeting inclusion criteria - other reasons (20: 34

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 187 patients assessed for eligibility and 177 patients excluded, so 10 patients enrolled for protocol treatment.

Period 1

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

Arms

Arm title	All patients

Arm description:

All registered subjects, planned to receive lapatinib in combination with oxaliplatin & capecitabine.

Arm type	Experimental
Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	Eloxatin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

"130 mg/m2 IV in 250-500 ml of 5% glucose over 2 hours (given once every 21 days for three cycles starting on day 11 of the trial)"

Investigational medicinal product name	capecitabine
Investigational medicinal product code	
Other name	Xeloda
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

850mg/m2 b.i.d po for 14 days.

Investigational medicinal product name	850mg/m2 b.i.d po for 14 days
Investigational medicinal product code	
Other name	Tyverb
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

1250 mg od po for days 1-72

Number of subjects in period 1	All patients
Started	10
10-day Induction period	10
Proceeded with surgery	9
Completed	7
Not completed	3
Consent withdrawn by subject	1
Adverse event, non-fatal	2

Baseline characteristics

Reporting groups	
Reporting group title	On-Study

Reporting group description: -

Reporting group values	On-Study	Total	
Number of subjects	10	10	
Age categorical			
All registered subjects, planned to receive lapatinib in combination with oxaliplatin & capecitabine.			
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)	6	6	
From 65-84 years	4	4	
85 years and over	0	0	
Age continuous			
All registered subjects, planned to receive lapatinib in combination with oxaliplatin & capecitabine			
Units: years			
arithmetic mean	61.7		
standard deviation	± 9.4	-	
Gender categorical			
All registered subjects, planned to receive lapatinib in combination with oxaliplatin & capecitabine.			
Units: Subjects			
Female	3	3	
Male	7	7	
Disease Site			
Site of primary disease.			
Units: Subjects			
Oesophagus	3	3	
Stomach	1	1	
Oesophago-gastric Junction (OGJ) Type I	1	1	
Oesophago-gastric Junction (OGJ) Type II	3	3	
Oesophago-gastric Junction (OGJ) Type III	2	2	

End points

End points reporting groups

Reporting group title	All patients

Reporting group description:

All registered subjects, planned to receive lapatinib in combination with oxaliplatin & capecitabine.

Subject analysis set title	All
Subject analysis set type	Full analysis

Subject analysis set description:

All registered subjects, planned to receive lapatinib in combination with oxaliplatin & capecitabine.

Primary: Molecular response

End point title	Molecular response[1]

End point description:

Concordance between molecular response in biopsies taken pre treatment and treated with lapatinib ex vivo and molecular response in a biopsy taken after 10 days of oral lapatinib in vivo (based on P-HER-2 staining on IHC only)

End point type	Primary

End point timeframe:

From pre-treatment to 10 days post-treatment with lapatinib

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: This is a single arm study. The summary of primary endpoints are provided.

End point values	All patients	All		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	9	9		
Units: subjects				
number (confidence interval 95%)				
Same Response	0.55 (0.2449 to 0.9148)	0.55 (0.2449 to 0.9148)		

Attachments (see zip file)	LEO SAE Listing/LEO SAE listing EudraCT 2010-019602-16.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Response on FGD-PET (SUV Max)

End point title	Response on FGD-PET (SUV Max)

End point description:

Perecentage of responders on FDG-PET based on reduction of >35% in Standard Uptake Variable (SUV) Maximal from central review .

End point type	Secondary

End point timeframe:

Please provide the time frame: it is requied for the end point definition.

End point values	All			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: subjects				
Non-Responder	9			
Responder	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Response on FGD-PET (SUV Average)

End point title	Response on FGD-PET (SUV Average)

End point description:

Perecentage of responders on FDG-PET based on reduction of >35% in Standard Uptake Variable (SUV) Average from central review.

End point type	Secondary

End point timeframe:

Please provide the time frame: it is requied for the end point definition

End point values	All			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: subjects				
Non-Responder	9			
Responder	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Radiological Response

End point title	Objective Radiological Response

End point description:

Objective Radiological Response by RECIST crieteria - Percentage of responders.

End point type	Secondary

End point timeframe:

Please provide the time frame: it is requied for the end point definition

End point values	All			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: Subjects				
number (confidence interval 95%)				
Responder	0.5 (0.1871 to 0.8129)			

Statistical analyses

No statistical analyses for this end point

Secondary: R0 Resection

End point title	R0 Resection

End point description:

R0 Resection - Percentage of Responders.

End point type	Secondary

End point timeframe:

Please provide the time frame: it is requied for the end point definition.

End point values	All			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: Sujects				
number (confidence interval 95%)				
Responder	0.778 (0.3999 to 0.9719)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pathological Complete Response

End point title	Pathological Complete Response

End point description:

Pathological Complete Response - Percentage of Responders.

End point type	Secondary

End point timeframe:

Please provide the time frame: it is requied for the end point definition.

End point values	All			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: Subjects				
number (confidence interval 95%)				
Responder	0.333 (0.0749 to 0.7007)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall Survival (months) - calculated from date of registration to date of death from any cause; suviving patients are censored at the date last known alive.

End point type	Secondary

End point timeframe:

Please provide the time frame: it is requied for the end point definition.

End point values	All			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: Months				
median (inter-quartile range (Q1-Q3))				
Overall Survival	32.4573 (13.7319 to 32.4573)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival

End point title	Progression-Free Survival

End point description:

Progression-Free Survival (months) - calculated from date of registration to date of first progression or date of death from any cause, whichever occurs first; surviving patients without disease progression are censored at the date last known alive.

End point type	Secondary

End point timeframe:

Please provide the time frame: it is requied for the end point definition

End point values	All			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: Months				
median (inter-quartile range (Q1-Q3))				
Progression-Free Survival	21.2714 (12.9435 to 99999)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Date of patient registration onto the trial and continued until 21 days after the last study drug administration.

Assessment type	Systematic

Dictionary used

Dictionary name	NCI CTC
Dictionary version	3

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Serious adverse events are reported in the file found in the uploaded attachment.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 April 2011	Inclusion of standard statements regarding the submission of complaints from patients participating in clinical trials and clarification on compensation available to patients harmed during the trial.
10 November 2011	Addition of medication diary to help us to monitor medication compliance on the trial.
23 March 2012	change to exclusion criteria, dose modifications, additional blood test added and clarification of testing to be carried out on biopsies
13 September 2012	Update the CTA to chnages the manufacturer responsible for the certification of the finished IMP and update the marketing authorisation number for Tyverb (lapatinib).
11 December 2012	Changes to details regarding secondary objectives, dose modifications for Non Haematological toxicities, repeat biopsies, dose limiting toxicity, sample size and molecular testing on biopsies.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported