Clinical trial results:
Phase II clinical trial of capecitabine and oxaliplatin plus bevacizumab as neoadjuvant treatment for patients with previously untreated unresectable liver-only metastases from colorectal cancer

Summary

EudraCT number	2005-004505-29
Trial protocol	GB
Global end of trial date	10 February 2015

Results information

Result version number	v1 (current)
This version publication date	25 September 2016
First version publication date	25 September 2016

Trial information

Trial identification

Sponsor protocol code	2676

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Royal Marsden NHS Foundation Trust
Sponsor organisation address	Downs Road, Sutton, London, United Kingdom, sm2 5pt
Public contact	Jacqui Oates, Royal Marsden NHS Foundation Trust, 0208 661 3279, jacqui.oates@rmh.nhs.uk
Scientific contact	Dr Khurum Khan, Royal Marsden NHS Foundation Trust , 0208 661 3279 , jacqui.oates@rmh.nhs.uk

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	01 May 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 February 2015
Global end of trial reached?	Yes
Global end of trial date	10 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the response rate of patients with previously untreated unresectable liver-only metastases from colorectal cancer treated with neoadjuvant capecitabine and oxaliplatin plus bevacizumab.

Protection of trial subjects:

The rate of liver resection correlated significantly with objective response rates (ORRs) of neoadjuvant chemotherapy . FOLFOXIRI (5-FU–LV–oxaliplatin–irinotecan) as well as the addition of cetuximab to FOLFOX or FOLFIRI (LV–5-FU–irinotecan) in Kras wild-type population resulted in a higher response rate compared with two-drug chemotherapy regimens . These improved response rates led to an increased rate of surgical metastases resection. Bevacizumab did not significantly improve ORR when added to oxaliplatin–fluoropyrimidine compared with oxaliplatin or fluoropyrimidine alone, and there were no statistically significant differences in resection rates in patients treated with bevacizumab compared with placebo . Nevertheless, these are subgroup (post hoc) analyses nested in large randomised, controlled trials of unselected patients not limited to liver-only metastases.

As prospective bevacizumab data were lacking in this setting, a multicentre study of CAPOX (capecitabine–oxaliplatin) plus bevacizumab in patients with high-risk colorectal liver-only metastases (CLMs) considered to be unsuitable for upfront liver resection in order to assess the efficacy and safety of this approach was conducted. In our BOXER (bevacizumab, oxaliplatin, xeloda in unresectable liver metastases) study, CAPOX plus bevacizumab was used as it was considered an accepted first-line treatment of advanced CRC , and high-risk disease was based on large size, poorly located, multinodular, and synchronous presentation of liver metastases.

This was considered standard approach at the time and thus no additonal safety risks were anticipated. However, all the routine safety procedures such as standard dose reductions or interruptions were conducted according to standrard hospital policies; moreover, a Trial Management Group (TMG) examined the safety of the study on regular basis.

Ref: http://annonc.oxfordjournals.org.ezproxy.icr.ac.uk/content/22/9/2042.long

Background therapy:

Oxaliplatin (130 mg/m2) and bevacizumab (7.5 mg/kg) were administered i.v. on day 1 every 3 weeks. Capecitabine was given orally at a dose of 1700 mg/m2/day divided into two split doses for 14 days followed by 7 days' rest repeated every 3 weeks. Dose adjustment was made in the event of toxicity assessed according to National Cancer Institute—Common Terminology Criteria for Adverse Events (NCI–CTCAE) version 3.0.

Operability was reassessed every four cycles (12 weeks) with CT and MRI scans and this would then be rediscussed at liver MDT meetings. Nonprogressors who remained unresectable would proceed to a further four cycles of treatment.
surgery.

Patients deemed to be resectable would undergo surgery at an 8-week interval from last dose of bevacizumab (6 weeks from last dose of chemotherapy). Patients with in situ primary tumours could have either synchronous or staged resection of primary tumour and liver metastases as per local practice.
postoperative chemotherapy.

After recovery from surgery, patients received another 12 weeks of CAPOX plus bevacizumab at the same dose schedule as preoperative block.

Evidence for comparator: -	
Actual start date of recruitment	26 June 2006
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: 46
Worldwide total number of subjects	46
EEA total number of subjects	46

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)	26
From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Appropriate patients were identified through multi-disciplinary meetings, which included representation from all disciplines including oncology, radiotherapy, surgery, histopathology and radiology. Patients were also idenfitied from new patient clinics by the sub-investigators.

Period 1

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

Arms

Arm title	All Patients

Arm description:

capecitabine & oxaliplatin with bevacizumab

Arm type	single arm study
Investigational medicinal product name	bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab 7.5mg/kg every 3 weeks

Number of subjects in period 1	All Patients
Started	46
Completed	45
Not completed	1
Patient not eligible	1

Baseline characteristics

Reporting groups	
Reporting group title	Treatment

Reporting group description: -

Reporting group values	Treatment	Total	
Number of subjects	46	46	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
median	63		
full range (min-max)	29 to 78	-	
Gender categorical Units: Subjects			
Female	17	17	
Male	29	29	

End points

End points reporting groups

Reporting group title	All Patients
Reporting group description: capecitabine & oxaliplatin with bevacizumab	

Primary: Overall Response Rate

End point title	Overall Response Rate[1]
End point description: Sum of complete and partial responses	
End point type	Primary
End point timeframe: Best observed response rate	

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 phase II study with only one arm, so no statistical comparisons can be made. This phase II study was designed using the optimal two-stage design with A'Hern exact P value. The primary end point was the best achieved ORR, calculated as the sum of observed complete and partial responses. An ORR rate of 60% was considered acceptable (p1) and ORR rate of 40% was ruled out as unacceptable (p0).

End point values	All Patients			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Patients	35			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From start of treatment to 30 days post treatment end	
Adverse event reporting additional description:	
Grade 3-5 related to treatment	
Assessment type	Systematic

Dictionary used	
Dictionary name	No dictionary
Dictionary version	0

Reporting groups	
Reporting group title	All Patients
Reporting group description:	
All subjects receiving a study drug	

Serious adverse events	All Patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 46 (15.22%)		
number of deaths (all causes)	20		
number of deaths resulting from adverse events	0		
Vascular disorders			
Venous thrombosis			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Infection			
subjects affected / exposed	4 / 46 (8.70%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			

subjects affected / exposed	2 / 46 (4.35%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal perforation			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All Patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 46 (52.17%)		
Nervous system disorders			
Peripheral neuropathy			
subjects affected / exposed	5 / 46 (10.87%)		
occurrences (all)	5		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	4 / 46 (8.70%)		
occurrences (all)	4		
General disorders and administration site conditions			
Lethargy			
subjects affected / exposed	11 / 46 (23.91%)		
occurrences (all)	11		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 46 (13.04%)		
occurrences (all)	6		
Skin and subcutaneous tissue disorders			
Hand and foot syndrome			
subjects affected / exposed	4 / 46 (8.70%)		
occurrences (all)	4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 July 2006	dose of capecitabine/oxaliplatin in combination chemotherapy reduced to 1700mg/m2 in two divided doses D1-14 in keeping with hospital guidelines
01 November 2007	dose adjustements for chemotherapy in patients above 75 years of age in keeping with the local guildelines
02 September 2009	clarification on follow up details on the study and additional PIS for patients participating in translational substudy

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

single arm non-randomised syudy with no comparatar arm

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/2128