Clinical trial results:
A phase II Trial to evaluate the efficacy and safety of Bevacizumab in combination with Capecitabine (Xeloda) in frail patients with untreated metastatic colorectal cancer

Summary

EudraCT number	2007-002682-12
Trial protocol	IE
Global end of trial date	16 January 2017

Results information

Result version number	v1 (current)
This version publication date	22 April 2018
First version publication date	22 April 2018

Trial information

Trial identification

Sponsor protocol code	ICORG 06-11 TORI GI-04

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Cancer Trials Ireland
Sponsor organisation address	Innovation House, Old Finglas Road, Dublin, Ireland, D11 KXN4
Public contact	Anna Shevlin, Cancer Trials Ireland, anna.shevlin@cancertrials.ie
Scientific contact	Anna Shevlin, Cancer Trials Ireland, anna.shevlin@cancertrials.ie

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	30 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 January 2017
Global end of trial reached?	Yes
Global end of trial date	16 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

•To determine the anti-tumor activity of bevacizumab plus capecitabine based on time to disease progression
•To evaluate the tolerability of bevacizumab plus capecitabine treatment in a patient population that is elderly or frail (poor performance)

Protection of trial subjects:

This clinical study was designed, implemented, and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations SI 190 of 2004 as amend and European Directive 2001/20/EC. The study was approved by the HPRA and SJH/AMNCH Research Ethics Committee.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 October 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Ireland: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	1

From 65 to 84 years	29
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was enrolled in Oct 2008, 30 patients were recruited. The last patient was recruited Aug 2012.

Pre-assignment

Screening details:

The target population will be all ECOG 2 metastatic colorectal cancer patients who require chemotherapy but are deemed too frail by their oncologist to tolerate combination chemotherapy with either irinotecan or oxaliplatin.

Period 1

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

Arms

Arm title	Overall trial

Arm description:

Untreated metastatic colorectal cancer patients who require chemotherapy but are deemed too frail by their oncologist to tolerate combination chemotherapy with either irinotecan or oxaliplatin.

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

Dosage and administration details:

Bevacizumab 7.5 mg/kg IV will be administered every 3 weeks. Administration will be as a continuous IV infusion.

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

Dosage and administration details:

Xeloda will be given as standard of care. The dose of Xeloda that will be used in this study is 1000mg/m2 administered orally twice daily (morning and evening, equivalent to 2000mg/m2 per day) for 2 weeks followed by 1 week of rest period given as a 3 week cycles. Xeloda tablets should be swallowed with water within 30 minutes after a meal.

Number of subjects in period 1	Overall trial
Started	30
Completed	30

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	30	30	
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	1	
From 65-84 years	29	29	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	76.2		
standard deviation	± 5.1	-	
Gender categorical Units: Subjects			
Female	12	12	
Male	18	18	
Ethnic origin Units: Subjects			
Caucasian	30	30	

End points

End points reporting groups

Reporting group title	Overall trial

Reporting group description:

Untreated metastatic colorectal cancer patients who require chemotherapy but are deemed too frail by their oncologist to tolerate combination chemotherapy with either irinotecan or oxaliplatin.

Primary: Progression-Free Survival

End point title	Progression-Free Survival[1]

End point description:

End point type	Primary

End point timeframe:

Time from registration to the first documented date of disease progression or death due to cancer.

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: The primary objective in this trial was to analyse progression free survival. Only 30/50 planned patients were enrolled in the Irish sites. Due to the reduced sample size, the original planned tests could not be carried out.

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: Months				
median (confidence interval 95%)	7.6 (4.3 to 11.2)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

November 2008 – November 2017 (9 years)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Study population

Reporting group description:

Untreated metastatic colorectal cancer patients who require chemotherapy but are deemed too frail by their oncologist to tolerate combination chemotherapy with either irinotecan or oxaliplatin.

Serious adverse events	Study population		
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 30 (66.67%)		
number of deaths (all causes)	29		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colorectal cancer metastatic			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant neoplasm progression			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombosis			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Salpingo-oophorectomy bilateral			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sudden death			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Atrioventricular block first degree			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Haemorrhage intracranial			

subjects affected / exposed	1 / 30 (3.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lethargy				
subjects affected / exposed	1 / 30 (3.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Neutropenia				
subjects affected / exposed	1 / 30 (3.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Diarrhoea				
subjects affected / exposed	3 / 30 (10.00%)			
occurrences causally related to treatment / all	5 / 5			
deaths causally related to treatment / all	0 / 0			
Abdominal hernia perforation				
subjects affected / exposed	1 / 30 (3.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	1 / 30 (3.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	1 / 30 (3.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorder				
subjects affected / exposed	1 / 30 (3.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				

subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Enteritis infectious			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			

Dehydration			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Study population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 30 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	5		
Hypotension			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	19 / 30 (63.33%)		
occurrences (all)	44		
Pyrexia			
subjects affected / exposed	6 / 30 (20.00%)		
occurrences (all)	6		
Mucosal inflammation			
subjects affected / exposed	6 / 30 (20.00%)		
occurrences (all)	7		
Pain			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Chest pain			

subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Injection site bruising			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Oedema peripheral			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 30 (23.33%)		
occurrences (all)	13		
Dyspnoea			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	6		
Dysphonia			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	8		
Epistaxis			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	7		
Rhinorrhoea			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Productive cough			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Wheezing			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Depressed mood			

subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2		
Investigations Weight decreased subjects affected / exposed occurrences (all) Blood bilirubin increased subjects affected / exposed occurrences (all) Haemoglobin decreased subjects affected / exposed occurrences (all)	 7 / 30 (23.33%) 8 4 / 30 (13.33%) 9 3 / 30 (10.00%) 4		
Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Hypoaesthesia subjects affected / exposed occurrences (all)	 4 / 30 (13.33%) 4 3 / 30 (10.00%) 3 3 / 30 (10.00%) 3 2 / 30 (6.67%) 2		
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all)	 3 / 30 (10.00%) 4		
Eye disorders Lacrimation increased subjects affected / exposed occurrences (all) Eye pain subjects affected / exposed occurrences (all)	 6 / 30 (20.00%) 6 2 / 30 (6.67%) 2		
Gastrointestinal disorders			

Diarrhoea subjects affected / exposed occurrences (all)	15 / 30 (50.00%) 41		
Nausea subjects affected / exposed occurrences (all)	13 / 30 (43.33%) 20		
Abdominal pain subjects affected / exposed occurrences (all)	9 / 30 (30.00%) 18		
Constipation subjects affected / exposed occurrences (all)	9 / 30 (30.00%) 14		
Vomiting subjects affected / exposed occurrences (all)	8 / 30 (26.67%) 12		
Dyspepsia subjects affected / exposed occurrences (all)	3 / 30 (10.00%) 3		
Stomatitis subjects affected / exposed occurrences (all)	3 / 30 (10.00%) 10		
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2		
Mouth ulceration subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2		
Tongue coated subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2		
Toothache subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 4		
Skin and subcutaneous tissue disorders Palmar-plantar erythrodysaesthesia syndrome			

subjects affected / exposed	15 / 30 (50.00%)		
occurrences (all)	41		
Rash			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	6		
Dry skin			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Pruritus			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Alopecia			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	5		
Dermatitis acneiform			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	3		
Laceration			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	7 / 30 (23.33%)		
occurrences (all)	9		
Arthralgia			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	7		
Pain in extremity			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	6		
Neck pain			

subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Muscular weakness			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Musculoskeletal pain			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	6 / 30 (20.00%)		
occurrences (all)	7		
Urinary tract infection			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	5		
Infection			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	9 / 30 (30.00%)		
occurrences (all)	21		
Dehydration			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 December 2007	Amendment #3 First version of the protocol applicable to Ireland
01 April 2008	Amendment #4: Modifications have been made to comply with HPRA requirements, ICH-GCP guidelines and to reflect procedures relevant to the Irish setting. Study medication, safety reporting of adverse events, retention of records and accrual target revised. Addition of: Study Schema, Study Synopsis, Investigator's Agreement, List of Abbreviations and Appendices.
01 July 2008	Amendment #5: Changes to study flow chart, evaluations during treatment and frailty markers.
25 November 2008	Amendment #6: Inclusion criteria, sample collection section and section 6.1.3 Bevacizumab Dose Modification and Toxicity Management updated. Addition of section 7.4 Follow-up. Administrative changes throughout the protocol.
20 August 2009	Amendment #7: Protocol updated and re-formatted to reflect updated Sponsor procedures. The translational sub-study, study medications, patient enrollment and safety sections and appendices were updated. Site Withdrawals/Change of PI added.

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.

The primary objective in this trial was to analyse progression free survival. Only 30/50 planned patients were enrolled in the Irish sites. Due to the reduced sample size, the original planned tests could not be carried out.

Notes: