



## 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
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##### 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

<b>Arm title</b>	Overall trial
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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/m<sup>2</sup> administered orally twice daily (morning and evening, equivalent to 2000mg/m<sup>2</sup> 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.

<b>Number of subjects in period 1</b>	Overall trial
Started	30
Completed	30



## Baseline characteristics

### Reporting groups

Reporting group title	Overall trial
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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 <sup>[1]</sup>
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End point description:

End point type	Primary
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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.

<b>End point values</b>	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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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### Reporting groups

Reporting group title	Study population
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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.

<b>Serious adverse events</b>	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		
<b>Surgical and medical procedures</b>			
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		
<b>General disorders and administration site conditions</b>			
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		
<b>Respiratory, thoracic and mediastinal disorders</b>			
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		
<b>Psychiatric disorders</b>			
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		
<b>Injury, poisoning and procedural complications</b>			
Overdose			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
<b>Cardiac disorders</b>			
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		
<b>Nervous system disorders</b>			
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 %

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

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

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

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

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

## 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: