Clinical trial results:
Avastin and chemotherapy followed by a K-Ras stratified randomization to maintenance treatment for first line treatment of metastatic colorectal cancer

Summary

EudraCT number	2010-019815-40
Trial protocol	DK
Global end of trial date	01 October 2014

Results information

Result version number	v1 (current)
This version publication date	09 May 2020
First version publication date	09 May 2020
Summary attachment (see zip file)	Summary (ACT2.Annals of Oncology.pdf)

Trial information

Trial identification

Sponsor protocol code	ML25359

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01229813
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Lund University Hospital
Sponsor organisation address	Getingevägen 4, Lund, Sweden, SE-221 85
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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	01 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 October 2014
Global end of trial reached?	Yes
Global end of trial date	01 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that maintenance treatment with bevacizumab + erlotinib following 1st line chemo- and anti-angiogenic therapy results in a significant increase in progression-free survival (PFS) rate at 3 months among patients without KRAS mutation as compared to maintenance treatment with bevacizumab alone.

Protection of trial subjects:

Adverse drug reactions, averse events and laboratory tests was graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0
Adverse events was monitored continuously during the treatment phase and for 28 days after the last intake/infusion of study drug.
Haematology and blood chemistry was performed 7 days before treatment start (Day -7 to 1), prior to each treatment cycle and at the final visit. Proteinuria (dipstick urinalysis) was performed within 48 hours prior to each bevacizumab dose.
Blood pressures was assessed on the first day of each treatment cycle.
Electrocardiogram (ECG) was performed at baseline and as clinically indicated.
The trial was performed according to ICH-GCP guidelines, as well as the Declaration of Helsinki.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	01 October 2010
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	Sweden: 213
Country: Number of subjects enrolled	Denmark: 20
Worldwide total number of subjects	233
EEA total number of subjects	233

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)	152
From 65 to 84 years	81
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Numbers of patients included in the trial is 233. These patients received induction treatment with chemotherapy according to investigator's choice for 6 or 9 cycles depending on regimen. Thereafter patients were randomised.

Pre-assignment

Screening details:

Study started after completed induction chemotherapy, where patients were randomised to 4 arms of maintenance treatment.

Pre-assignment period milestones

Number of subjects started	138[1]
Number of subjects completed	138[2]

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: Not all patients were randomized; 93 patients did not start maintenance treatment due to progressive disease, or surgery with curative intension.
[2] - The number of subjects reported to be in the pre-assignment period is not consistent with the number starting period 1. It is expected that the number completing the pre-assignment period are also present in the arms in period 1.
Justification: All patients were not randomised due to progressive disease, or suitable for surgery with curative intent efter induction therapy.

Period 1

Period 1 title	Start of maintenance treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	wt-BE

Arm description:

Maintenance treatment with bevacizumab intravenously every third week and erlotinib orally every day.

Arm type	Active comparator
Investigational medicinal product name	bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Powder for dispersion for infusion
Routes of administration	Intravenous use

Dosage and administration details:

7.5 mg/kg body weight intravenously every third week.

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

Dosage and administration details:

150 mg once daily.

Arm title	wt-B

Arm description:	
Bevacizumab intravenously every third week.	
Arm type	Active comparator
Investigational medicinal product name	erlotinib
Investigational medicinal product code	
Other name	Tarceva
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
150 mg once daily.	
Arm title	mut-B
Arm description:	
Bevacizumab intravenously every third week.	
Arm type	Active comparator
Investigational medicinal product name	bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details:	
7.5 mg/ kg body weight intravenously every third week.	
Arm title	mut-C
Arm description:	
Capecitabine orally, 500 mg, twice Daily.	
Arm type	Active comparator
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:	
500 mg orally twice daily.	

Number of subjects in period 1	wt-BE	wt-B	mut-B
Started	36	35	34
Completed	36	35	34

Number of subjects in period 1	mut-C
Started	33
Completed	33

Baseline characteristics

Reporting groups[1]	
Reporting group title	wt-BE
Reporting group description:	
Maintenance treatment with bevacizumab intravenously every third week and erlotinib orally every day.	
Reporting group title	wt-B
Reporting group description:	
Bevacizumab intravenously every third week.	
Reporting group title	mut-B
Reporting group description:	
Bevacizumab intravenously every third week.	
Reporting group title	mut-C
Reporting group description:	
Capecitabine orally, 500 mg, twice Daily.	

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: Not all patients were randomized; 93 patients did not start maintenance treatment due to progressive disease, or surgery with curative intension.

Reporting group values	wt-BE	wt-B	mut-B
Number of subjects	36	35	34
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	20	22	18
From 65-84 years	16	13	16
85 years and over	0	0	0
Adults	0	0	0
Age continuous			
Units: years			
median	65	61	65
full range (min-max)	38 to 74	32 to 76	44 to 75
Gender categorical			
Units: Subjects			
Female	14	13	13
Male	22	22	21

Reporting group values	mut-C	Total	
Number of subjects	33	138	
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)	20	80	
From 65-84 years	13	58	
85 years and over	0	0	
Adults	0	0	
Age continuous			
Units: years			
median	63		
full range (min-max)	45 to 79	-	
Gender categorical			
Units: Subjects			
Female	13	53	
Male	20	85	

Subject analysis sets

Subject analysis set title	Progression free survival
Subject analysis set type	Full analysis

Subject analysis set description:

Patients who started maintenance treatment, with no progressive disease, or were suitable for surgery with curative intention.

Reporting group values	Progression free survival		
Number of subjects	138		
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)	80		
From 65-84 years	58		
85 years and over	0		
Adults	0		
Age continuous			
Units: years			
median	64		
full range (min-max)	32 to 79		
Gender categorical			
Units: Subjects			
Female	53		
Male	85		

End points

End points reporting groups

Reporting group title	wt-BE
Reporting group description:	
Maintenance treatment with bevacizumab intravenously every third week and erlotinib orally every day.	
Reporting group title	wt-B
Reporting group description:	
Bevacizumab intravenously every third week.	
Reporting group title	mut-B
Reporting group description:	
Bevacizumab intravenously every third week.	
Reporting group title	mut-C
Reporting group description:	
Capecitabine orally, 500 mg, twice Daily.	
Subject analysis set title	Progression free survival
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients who started maintenance treatment, with no progressive disease, or were suitable for surgery with curative intention.	

Primary: Progression Free Survival (PFS) defined as the time from randomisation until date of progression or death from any cause.

End point title	Progression Free Survival (PFS) defined as the time from randomisation until date of progression or death from any cause.
End point description:	
End point type	Primary
End point timeframe:	
Was evaluated every nine week during the trial.	

End point values	wt-BE	wt-B	mut-B	mut-C
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	36	35	34	33
Units: Months				
number (not applicable)	36	35	34	33

End point values	Progression free survival			
Subject group type	Subject analysis set			
Number of subjects analysed	138			
Units: Months				
number (not applicable)	138			

Statistical analyses

Statistical analysis title	Log rank test.
Comparison groups	wt-BE v wt-B v mut-B v mut-C v Progression free survival
Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Logrank

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From start of treatment, and 28 days after end of treatment.	
Assessment type	Systematic

Dictionary used	
Dictionary name	NCI-CTCAE
Dictionary version	3.0

Reporting groups	
Reporting group title	All patients

Reporting group description:

Infections and infestations 32
General disorders and administration site disorders 5
Gastrointestinal disorcders 75
Cardiac disorders 4
Investigations 6
Respiratory, thoracic and mediastinal disorders 6
Nervous system disorders 1
Vascular disorders 14
Immune system disorders 1
Psychiatric disorders 2
Musculoskeletal and connective tissue disorders 1
Skin and subcutaneous tissue disorders 1

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	81 / 231 (35.06%)		
number of deaths (all causes)	8		
number of deaths resulting from adverse events	0		
Investigations			
Creatinine increased			
subjects affected / exposed	2 / 231 (0.87%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Liver disorder			
subjects affected / exposed	3 / 231 (1.30%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Blood glucose increased			
subjects affected / exposed	1 / 231 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Vascular disorders			
Embolism venous			
subjects affected / exposed	10 / 231 (4.33%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 2		
Embolism arterial			
subjects affected / exposed	2 / 231 (0.87%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Cardiac disorders			
Cardiac disorder			
subjects affected / exposed	6 / 231 (2.60%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Anxiety disorder			
subjects affected / exposed	1 / 231 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral infarction			
subjects affected / exposed	1 / 231 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
General disorders and administration site conditions			
Allergic transfusion reaction			
subjects affected / exposed	3 / 231 (1.30%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 231 (1.73%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Vomiting			

subjects affected / exposed	7 / 231 (3.03%)			
occurrences causally related to treatment / all	7 / 7			
deaths causally related to treatment / all	0 / 0			
Perforation				
subjects affected / exposed	6 / 231 (2.60%)			
occurrences causally related to treatment / all	6 / 6			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	2 / 231 (0.87%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	9 / 231 (3.90%)			
occurrences causally related to treatment / all	0 / 9			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	9 / 231 (3.90%)			
occurrences causally related to treatment / all	0 / 9			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	1 / 231 (0.43%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Pulmonary lymphangiectasia				
subjects affected / exposed	1 / 231 (0.43%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Infections and infestations				
infection with normal ANC				
subjects affected / exposed	8 / 231 (3.46%)			
occurrences causally related to treatment / all	5 / 8			
deaths causally related to treatment / all	0 / 0			

Infection with unknown ANC			
subjects affected / exposed	2 / 231 (0.87%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 231 (0.87%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	1 / 231 (0.43%)		
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	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	148 / 231 (64.07%)		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	13 / 231 (5.63%)		
occurrences (all)	13		
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	1 / 231 (0.43%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	13 / 231 (5.63%)		
occurrences (all)	13		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	10 / 231 (4.33%)		
occurrences (all)	10		
Depression			

subjects affected / exposed	7 / 231 (3.03%)		
occurrences (all)	7		
Confusional state			
subjects affected / exposed	2 / 231 (0.87%)		
occurrences (all)	2		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 231 (1.73%)		
occurrences (all)	4		
Hypomagnesaemia			
subjects affected / exposed	1 / 231 (0.43%)		
occurrences (all)	1		
Blood potassium decreased			
subjects affected / exposed	2 / 231 (0.87%)		
occurrences (all)	2		
Blood sodium decreased			
subjects affected / exposed	1 / 231 (0.43%)		
occurrences (all)	1		
Blood creatinine increased			
subjects affected / exposed	8 / 231 (3.46%)		
occurrences (all)	8		
Blood bilirubin increased			
subjects affected / exposed	2 / 231 (0.87%)		
occurrences (all)	2		
White blood cell count decreased			
subjects affected / exposed	4 / 231 (1.73%)		
occurrences (all)	4		
Blood albumin decreased			
subjects affected / exposed	3 / 231 (1.30%)		
occurrences (all)	3		
Blood glucose increased			
subjects affected / exposed	3 / 231 (1.30%)		
occurrences (all)	3		
Cardiac murmur			
subjects affected / exposed	1 / 231 (0.43%)		
occurrences (all)	1		

Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 231 (0.43%)		
occurrences (all)	1		
Arrhythmia			
subjects affected / exposed	3 / 231 (1.30%)		
occurrences (all)	3		
Atrial fibrillation			
subjects affected / exposed	2 / 231 (0.87%)		
occurrences (all)	2		
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 231 (0.43%)		
occurrences (all)	1		
Balance disorder			
subjects affected / exposed	2 / 231 (0.87%)		
occurrences (all)	2		
Convulsion			
subjects affected / exposed	1 / 231 (0.43%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	16 / 231 (6.93%)		
occurrences (all)	16		
Dysgeusia			
subjects affected / exposed	54 / 231 (23.38%)		
occurrences (all)	54		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 231 (0.87%)		
occurrences (all)	2		
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 231 (0.43%)		
occurrences (all)	1		
Gastrointestinal disorders			
Nausea			

subjects affected / exposed	50 / 231 (21.65%)		
occurrences (all)	173		
Constipation			
subjects affected / exposed	55 / 231 (23.81%)		
occurrences (all)	55		
Abdominal pain			
subjects affected / exposed	70 / 231 (30.30%)		
occurrences (all)	70		
Flatulence			
subjects affected / exposed	6 / 231 (2.60%)		
occurrences (all)	6		
Ileus			
subjects affected / exposed	12 / 231 (5.19%)		
occurrences (all)	12		
Subileus			
subjects affected / exposed	9 / 231 (3.90%)		
occurrences (all)	9		
Dysphagia			
subjects affected / exposed	1 / 231 (0.43%)		
occurrences (all)	1		
Anal pruritus			
subjects affected / exposed	1 / 231 (0.43%)		
occurrences (all)	1		
Haemorrhoids			
subjects affected / exposed	5 / 231 (2.16%)		
occurrences (all)	5		
Ascites			
subjects affected / exposed	1 / 231 (0.43%)		
occurrences (all)	1		
Abdominal distension			
subjects affected / exposed	2 / 231 (0.87%)		
occurrences (all)	2		
Colonic obstruction			
subjects affected / exposed	1 / 231 (0.43%)		
occurrences (all)	1		
Hepatobiliary disorders			

Biliary colic			
subjects affected / exposed	1 / 231 (0.43%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Skin hyperpigmentation			
subjects affected / exposed	4 / 231 (1.73%)		
occurrences (all)	4		
Alopecia			
subjects affected / exposed	28 / 231 (12.12%)		
occurrences (all)	28		
Acne			
subjects affected / exposed	5 / 231 (2.16%)		
occurrences (all)	5		
Decubitus ulcer			
subjects affected / exposed	1 / 231 (0.43%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 231 (0.43%)		
occurrences (all)	1		
Infections and infestations			
Infection			
subjects affected / exposed	27 / 231 (11.69%)		
occurrences (all)	27		
Urinary tract infection			
subjects affected / exposed	27 / 231 (11.69%)		
occurrences (all)	27		
Periodontitis			
subjects affected / exposed	1 / 231 (0.43%)		
occurrences (all)	1		
Otitis media			
subjects affected / exposed	1 / 231 (0.43%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	5 / 231 (2.16%)		
occurrences (all)	5		

Clostridial infection				
subjects affected / exposed	1 / 231 (0.43%)			
occurrences (all)	1			
Tooth infection				
subjects affected / exposed	1 / 231 (0.43%)			
occurrences (all)	1			
Gastroenteritis				
subjects affected / exposed	1 / 231 (0.43%)			
occurrences (all)	1			
Herpes zoster				
subjects affected / exposed	3 / 231 (1.30%)			
occurrences (all)	3			
Skin infection				
subjects affected / exposed	2 / 231 (0.87%)			
occurrences (all)	2			
Anal abscess				
subjects affected / exposed	1 / 231 (0.43%)			
occurrences (all)	1			
Fungal infection				
subjects affected / exposed	2 / 231 (0.87%)			
occurrences (all)	2			
Influenza				
subjects affected / exposed	1 / 231 (0.43%)			
occurrences (all)	1			
Gingivitis				
subjects affected / exposed	1 / 231 (0.43%)			
occurrences (all)	1			
Arthritis bacterial				
subjects affected / exposed	1 / 231 (0.43%)			
occurrences (all)	1			
Borrelia infection				
subjects affected / exposed	1 / 231 (0.43%)			
occurrences (all)	1			
Abdominal infection				
subjects affected / exposed	1 / 231 (0.43%)			
occurrences (all)	1			

Device related infection subjects affected / exposed occurrences (all)	5 / 231 (2.16%) 5		
Ear infection subjects affected / exposed occurrences (all)	2 / 231 (0.87%) 2		
Enterocolitis infectious subjects affected / exposed occurrences (all)	1 / 231 (0.43%) 1		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	56 / 231 (24.24%) 56		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 January 2012	Increase of numbers of patients to be included (from 181 to 230). It was assumed that 70 % of the patients would fulfil all criteria for randomization to maintenance treatment. Only 60 % of the population could be randomized to the different arms of maintenance treatment, mostly because of progressive disease during chemotherapy, and surgery with curative intention. To maintain the statistical strength, 49 additional patients needed to be enrolled.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26483047