Clinical trial results:
Continous treatment with bevacizumab in elderly patients with mCRC: an open label, single arm, prospective phase IV trial to evaluate outcome and safety of continuous bevacizumab treatment in combination with chemotherapy over disease progression

Summary

EudraCT number	2014-003844-11
Trial protocol	SE
Global end of trial date	11 December 2018

Results information

Result version number	v1 (current)
This version publication date	27 December 2019
First version publication date	27 December 2019
Summary attachment (see zip file)	GRACE Clinical Study Report (GRACE Clinical Study Report-191206 - Slutversion.docx)

Trial information

Trial identification

Sponsor protocol code	ML29242

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Department of Oncology, Linköping University of Hospital
Sponsor organisation address	Linköping University of Hospital, Linköping, Sweden, 58185
Public contact	Gunnar Adell, Dept of Onc, Linköping Uni Hospital, Department of Oncology, Linköping University Hospital, +46 101030000, gunnar.adell@regionostergotland.se
Scientific contact	Gunnar Adell, Dept of Onc, Linköping Uni Hospital, Department of Oncology, Linköping University Hospital, +46 1010300000, gunnar.adell@regionostergotland.se

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	06 December 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 December 2018
Global end of trial reached?	Yes
Global end of trial date	11 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the feasibility of continous treatment with bevacizumab beyond disease progression in an elderly community based patient population by assessment of overall survival.

Protection of trial subjects:

Written informed consent was obtained from each patient participating in the study before any study specific screening procedure was performed. Informed consent was signed after adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study.
The investigator must assure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On eCRFs or other documents subjects should not be identified by their names but by an identification code. The investigator should keep a subject enrolment log showing codes, names and addresses in strict confidence.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 November 2015
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	Sweden: 48
Worldwide total number of subjects	48
EEA total number of subjects	48

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)	0
From 65 to 84 years	46

85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Recrutiment: 02nov2015 to 11dec2018

Pre-assignment

Screening details:

- Demographics and medical history – includes age, gender and current diseases
- Information on cancer and treatment history
- Concurrent disease – diseases potentially
- Physical examination and vital signs – include height, weight, pulse, blood pressure
- ECG

Pre-assignment period milestones

Number of subjects started	48
Number of subjects completed	48

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	bevacizumab

Arm description:

open label, singel arm

Arm type	single
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab was administered at a fixed dose equivalent to 2.5 mg/kg per week; either as 7.5 mg /kg every three weeks (q3w) or 5 mg/kg every two weeks (2qw). Bevacizumab is a concentrate that should be diluted with sodium chloride (NaCl) for intravenous infusions

Number of subjects in period 1	bevacizumab
Started	48
Completed	0
Not completed	48
Study terminated	22
Death	17
Protocol deviation	9

Baseline characteristics

Reporting groups

Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	48	48	
Age categorical			
The median (range) age was 76 (70-88) years.			
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)	0	0	
From 65-84 years	46	46	
85 years and over	2	2	
Age continuous			
The median (range) age was 76 (70-88) years.			
Units: years			
median	76		
standard deviation	± 18	-	
Gender categorical			
Units: Subjects			
Female	27	27	
Male	21	21	

Subject analysis sets

Subject analysis set title	overall survival
Subject analysis set type	Per protocol

Subject analysis set description:

Overall survival was measured as the time from the date of enrolment to the date of death. Patients without death date were censored at the date when the trial was terminated (11dec2018).

Reporting group values	overall survival		
Number of subjects	39		
Age categorical			
The median (range) age was 76 (70-88) years.			
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	46		
85 years and over	2		
Age continuous			
The median (range) age was 76 (70-88) years.			
Units: years			
median	17.4		
standard deviation	± 10.9		
Gender categorical			
Units: Subjects			
Female	16		
Male	23		

End points

End points reporting groups	
Reporting group title	bevacizumab
Reporting group description:	
open label, singel arm	
Subject analysis set title	overall survival
Subject analysis set type	Per protocol
Subject analysis set description:	
Overall survival was measured as the time from the date of enrolment to the date of death. Patients without death date were censored at the date when the trial was terminated (11dec2018).	

Primary: To assess overall Sutvival (OS) from time of inclusion	
End point title	To assess overall Sutvival (OS) from time of inclusion
End point description:	
To assess Overall survival (OS) from time of inclusion	
End point type	Primary
End point timeframe:	
Overall survival (OS) from time of inclusion	

End point values	bevacizumab	overall survival		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	39	39		
Units: percent				
number (not applicable)	39	39		

Statistical analyses

Statistical analysis title	kaplan-meier
Statistical analysis description:	
The main efficacy endpoint overall survival was estimated using the Kaplan-Meier method.	
Comparison groups	bevacizumab v overall survival
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0 [2]
Method	no comparison
Parameter estimate	Median difference (final values)
Point estimate	17.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.6
upper limit	22.3

Notes:
[1] - only description, no comparison
[2] - no comparison were made

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline to 30 Days after last dose of study treatment should be recorded

Adverse event reporting additional description:

Adverse events ≥ grade 3 and any grade ATEs experienced up until 30 days after the last dose of study treatment should be recorded in the eCRF and followed up until they have returned to baseline status or stabilized. All AEs ≥ grade 3 including any grade ATE considered related to bevacizumab which occur up to 6 months after the last dose should al

Assessment type	Non-systematic

Dictionary used

Dictionary name	NCI CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Bevacizumab

Reporting group description:

open label, singel arm

Serious adverse events	Bevacizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 48 (35.42%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
General disorders and administration site conditions			
pain	Additional description: pain in abdomen or back		
subjects affected / exposed	5 / 48 (10.42%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Rectal perforation	Additional description: rectal perforation		
subjects affected / exposed	2 / 48 (4.17%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	1 / 1		
rectal hemorrhage	Additional description: rectal hemorrhage		
subjects affected / exposed	2 / 48 (4.17%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Colitis	Additional description: colitis		

subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ileal fistula	Additional description: ileal fistula		
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infection	Additional description: infection with fever		
subjects affected / exposed	6 / 48 (12.50%)		
occurrences causally related to treatment / all	2 / 6		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Bevacizumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 48 (8.33%)		
Injury, poisoning and procedural complications			
Pulmonary embolism	Additional description: pulmonary embolism		
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Vascular disorders			
Hypertension	Additional description: Hypertension		
subjects affected / exposed	2 / 48 (4.17%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
anemia	Additional description: anemia		
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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.

100 patients were planned to be enrolled, allowing a drop-out rate of 10%. Estimated accrual time of 36 months. The study was early terminated at 37 months after study initiation and after 48 patients had been included, of which 19% dropped- out. The

Notes: