Clinical trial results:
A Phase II pilot study to assess efficacy and safety of capecitabine and irinotecan plus bevacizumab followed by capecitabine and oxaliplatin plus bevacizumab or the reverse sequence in patients with metastatic colorectal cancer.

Summary

EudraCT number	2011-002191-16
Trial protocol	AT
Global end of trial date	31 August 2017

Results information

Result version number	v1 (current)
This version publication date	24 May 2019
First version publication date	24 May 2019

Trial information

Trial identification

Sponsor protocol code	ML25153

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02119026
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medizinische Universität Wien
Sponsor organisation address	Waehringer Guertel 18-20, Vienna, Austria, 1090
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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	06 March 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2017
Global end of trial reached?	Yes
Global end of trial date	31 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Determine the efficacy of modified XELIRI (Capecitabine and Irinotecan) in combination with bevacizumab followed by XELOX (Capecitabine and Oxaliplatin) in combination with bevacizumab at progression in comparison with the reverse sequence based on duration of disease control (DDC) .

Protection of trial subjects:

In case a patient experienced severe chemotherapy-related toxicity or progressive disease, Investigators were allowed to modify, change or interrupt the chemotherapy regimen as appropriate.
Patients received full supportive care including transfusion of blood products, antibiotics, antiemetic and pain treatment, where applicable.
Adverse events and adverse drug reactions were followed continuously throughout the study.

Background therapy:

Not applicable

Evidence for comparator:

Several phase II studies evaluated the safety and efficacy of adding bevacizumab to XELOX and XELIRI regimen in metastatic colorectal cancer. XELOX or XELIRI + bevacizumab have been investigated in several trials, but not in an approach with clearly defined cross-wise XELIRI-XELOX change criteria. The addition of bevacizumab to an approach with clearly defined cross-wise XELIRI-XELOX change criteria combined with the concept of maintenance therapy seemed an attractive option to improve the results for patients with metastatic colorectal cancer.

Actual start date of recruitment	12 April 2012
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	Austria: 120
Worldwide total number of subjects	120
EEA total number of subjects	120

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	51
From 65 to 84 years	69
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

FPI First patient in: 12-Apr-2012
LPI Last patient in: 23-Jan-2015
Last patient last visit LPLV: 31-Aug-2017
Assessed for eligibility: 126 patients
Eligible and randomized: 120 patients (58 in Arm A and 62 in Arm B)

Pre-assignment

Screening details:

126 patients with metastatic colorectal cancer (according to RECIST criteria) who did not receive systemic treatment for their metastatic disease were screened for eligibility.
6 patients did not meet inclusion criteria and/or met exclusion criteria.

Period 1

Period 1 title	1st-line treatment
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

1st-line treatment with XELIRI+Bevacizumab for 6 months (8 cycles): capecitabine : 800mg/m2 bid d1-14, bevacizumab 7,5 mg/kg given on day 1 q3w combined with irinotecan 200mg/m2 iv. d 1 q3w followed by maintenance treatment until progression: bevacizumab (7.5 mg/kg q3w) ± capecitabine (1000 mg/m2 bid, days 1-14 q3w); in case of progression followed by 2nd-line treatment XELOX+Bevacizumab for 4 months (6 cycles).

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:

800mg/m2 bid d1-14 for 6 months (8 cycles) and 1000 mg/m2 bid, days 1-14 q3w optional during maintenance treatment until progression

Investigational medicinal product name	Bevcizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

7.5 mg/kg q3w for 8 cycles and during maintenance treatment until progression

Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Irinotecan 200mg/m2 iv. d 1 q3w for 6 months (8 cycles)

Arm title	Arm B

Arm description:

1st-line treatment with XELOX+Bevacizumab for 6 months (8 cycles): capecitabine 1000mg/m2 bid d1-14, bevacizumab 7,5 mg/kg given on d1 q3w combined with oxaliplatin 130mg/m2 iv. d 1 q3w followed by maintenance treatment until progression: bevacizumab (7.5 mg/kg q3w) ± capecitabine (1000 mg/m2 bid, days 1-14 q3w); in case of progression followed by 2nd-line treatment XELIRI+Bevacizumab for 4 months (6 cycles)

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:

1000mg/m2 bid d1-14 for 6 months (8 cycles) and 1000 mg/m2 bid, days 1-14 q3w optional during maintenance treatment until progression

Investigational medicinal product name	Bevcizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

7.5 mg/kg q3w for 8 cycles and during maintenance treatment until progression

Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

130mg/m2 iv. d 1 q3w for 6 months (8 cycles)

Number of subjects in period 1	Arm A	Arm B
Started	58	62
Completed	30	24
Not completed	28	38
Adverse event, serious fatal	3	6
Consent withdrawn by subject	4	10
Physician decision	4	8
Surgery of metastases	1	-
Adverse event, non-fatal	6	8
Patient condition	3	4
Complete remission until EOS	1	1
Lost to follow-up	2	-
Lack of efficacy	3	1
Protocol deviation	1	-

Period 2

Period 2 title	2nd-line treatment
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

2nd-line treatment XELOX+Bevacizumab for 4 months (6 cycles): capecitabine 1000mg/m2 bid d1-14, bevacizumab 7,5 mg/kg given on d1 q3w combined with oxaliplatin 130mg/m2 iv. d 1 q3w followed by maintenance treatment until progression: bevacizumab (7.5 mg/kg q3w) ± capecitabine (1000 mg/m2 bid, days 1-14 q3w)

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:

1000mg/m2 bid d1-14 for 4 months (6 cycles) and optional during maintenance treatment until progression

Investigational medicinal product name	Bevcizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

7.5 mg/kg q3w for 6 cycles and during maintenance treatment until progression

Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

130mg/m2 iv. d 1 q3w for 4 months (6 cycles)

Arm title	Arm B

Arm description:

2nd-line treatment XELIRI+Bevacizumab for 4 months (6 cycles): capecitabine : 800mg/m2 bid d1-14, bevacizumab 7,5 mg/kg given on day 1 q3w combined with irinotecan 200mg/m2 iv. d 1 q3w followed by maintenance treatment until progression: bevacizumab (7.5 mg/kg q3w) ± capecitabine (1000 mg/m2 bid, days 1-14 q3w)

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:	
800mg/m2 bid d1-14 for 4 months (6 cycles) and 1000 mg/m2 bid, days 1-14 q3w optional during maintenance treatment until progression	
Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Irinotecan 200mg/m2 iv. d 1 q3w for 4 months (6 cycles)	
Investigational medicinal product name	Bevcizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
7.5 mg/kg q3w for 6 cycles and during maintenance treatment until progression	

Number of subjects in period 2	Arm A	Arm B
Started	30	24
Completed	23	22
Not completed	7	2
Consent withdrawn by subject	3	1
Adverse event, non-fatal	4	1

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description:	
1st-line treatment with XELIRI+Bevacizumab for 6 months (8 cycles): capecitabine : 800mg/m2 bid d1-14, bevacizumab 7,5 mg/kg given on day 1 q3w combined with irinotecan 200mg/m2 iv. d 1 q3w followed by maintenance treatment until progression: bevacizumab (7.5 mg/kg q3w) ± capecitabine (1000 mg/m2 bid, days 1-14 q3w); in case of progression followed by 2nd-line treatment XELOX+Bevacizumab for 4 months (6 cycles).	
Reporting group title	Arm B
Reporting group description:	
1st-line treatment with XELOX+Bevacizumab for 6 months (8 cycles): capecitabine 1000mg/m2 bid d1-14, bevacizumab 7,5 mg/kg given on d1 q3w combined with oxaliplatin 130mg/m2 iv. d 1 q3w followed by maintenance treatment until progression: bevacizumab (7.5 mg/kg q3w) ± capecitabine (1000 mg/m2 bid, days 1-14 q3w); in case of progression followed by 2nd-line treatment XELIRI+Bevacizumab for 4 months (6 cycles)	

Reporting group values	Arm A	Arm B	Total
Number of subjects	58	62	120
Age categorical			
Inclusion criterion: age equal or above 18; no upper limit			
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)	22	29	51
From 65-84 years	36	33	69
85 years and over	0	0	0
Gender categorical			
not applicable			
Units: Subjects			
Female	19	19	38
Male	39	43	82

End points

End points reporting groups

Reporting group title	Arm A

Reporting group description:

1st-line treatment with XELIRI+Bevacizumab for 6 months (8 cycles): capecitabine : 800mg/m2 bid d1-14, bevacizumab 7,5 mg/kg given on day 1 q3w combined with irinotecan 200mg/m2 iv. d 1 q3w followed by maintenance treatment until progression: bevacizumab (7.5 mg/kg q3w) ± capecitabine (1000 mg/m2 bid, days 1-14 q3w); in case of progression followed by 2nd-line treatment XELOX+Bevacizumab for 4 months (6 cycles).

Reporting group title	Arm B

Reporting group description:

1st-line treatment with XELOX+Bevacizumab for 6 months (8 cycles): capecitabine 1000mg/m2 bid d1-14, bevacizumab 7,5 mg/kg given on d1 q3w combined with oxaliplatin 130mg/m2 iv. d 1 q3w followed by maintenance treatment until progression: bevacizumab (7.5 mg/kg q3w) ± capecitabine (1000 mg/m2 bid, days 1-14 q3w); in case of progression followed by 2nd-line treatment XELIRI+Bevacizumab for 4 months (6 cycles)

Reporting group title	Arm A

Reporting group description:

2nd-line treatment XELOX+Bevacizumab for 4 months (6 cycles): capecitabine 1000mg/m2 bid d1-14, bevacizumab 7,5 mg/kg given on d1 q3w combined with oxaliplatin 130mg/m2 iv. d 1 q3w followed by maintenance treatment until progression: bevacizumab (7.5 mg/kg q3w) ± capecitabine (1000 mg/m2 bid, days 1-14 q3w)

Reporting group title	Arm B

Reporting group description:

2nd-line treatment XELIRI+Bevacizumab for 4 months (6 cycles): capecitabine : 800mg/m2 bid d1-14, bevacizumab 7,5 mg/kg given on day 1 q3w combined with irinotecan 200mg/m2 iv. d 1 q3w followed by maintenance treatment until progression: bevacizumab (7.5 mg/kg q3w) ± capecitabine (1000 mg/m2 bid, days 1-14 q3w)

Subject analysis set title	Arm A (1st- and 2nd-line treatment)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients randomized were included in the ITT population, if at least one dose of study medication was administered/taken after randomization.
Patients were assigned to treatment groups as randomized for analysis purposes.
The ITT population is used for the primary efficacy analysis (ITT analysis).
For analysis of this population treatment periods 1 and 2 are considered.

Subject analysis set title	Arm B (1st- and 2nd-line treatment)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients randomized were included in the ITT population, if at least one dose of study medication was administered/taken after randomization.
Patients were assigned to treatment groups as randomized for analysis purposes.
The ITT population is used for the primary efficacy analysis (ITT analysis).
For analysis of this population treatment periods 1 and 2 are considered.

Primary: Duration of disease control DDC

End point title	Duration of disease control DDC

End point description:

"Efficacy of modified XELIRI (Capecitabine and Irinotecan) in combination with bevacizumab followed by XELOX (Capecitabine and Oxaliplatin) in combination with bevacizumab at progression in comparison with the reverse sequence based on DDC."
The primary variable was duration of disease control (DDC) and was defined as the sum of progression free survival intervals during first line and second line treatment (= time from the beginning of first line treatment until onset of progression during second line treatment). Patients without progression at the last tumor assessment date during their study participation were censored at this last tumor assessment date (exception: availability of validated information about a later onset of progression or a longer progression free interval – in such a case the date of the follow-up assessment was either defined as the onset of progression or replaced the last tumor assessment date).

End point type	Primary

End point timeframe:

From treatment start 1st-line until progression 2nd-line

End point values	Arm A (1st- and 2nd-line treatment)	Arm B (1st- and 2nd-line treatment)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	58	62		
Units: Days				
median (confidence interval 95%)	373.000 (321.520 to 424.480)	370.000 (253.255 to 486.745)		

Attachments (see zip file)	Primary Endpoint DDC/1 Primary Endpoint DDC.pdf

Statistical analyses

Statistical analysis title	Efficacy analysis DDC

Statistical analysis description:

DDC between Arm A and Arm B. DDC was calculated by the Kaplan-Meier estimator and compared by using the Mantel-Haenszel-Log-Rank-Test. Power calculation was done too. In case of inhomogeneities of demographic or baseline variables across the arms these variables were examined in an exploratory way (proportional hazard Cox-Regression model, assumption of proportional hazards verified by Schoenfeld-residuals, time dependent Cox-Regression model, two-sided 95%-confidence-intervals for hazards)

Comparison groups	Arm B (1st- and 2nd-line treatment) v Arm A (1st- and 2nd-line treatment)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.967
Method	Mantel-Haenszel

Notes:

[1] - Given the data of the ITT population the study achieved a power of 63.08% for the primary endpoint “DDC (duration of disease control)” based on a sample-size-estimation algorithm for Mantel-Haenszel-Log-Rank-Test.
The data resulting from this pilot study can be used for the sample size estimation of a confirmatory trial which is designed either towards superiority or towards non-inferiority.

Secondary: First line PFS

End point title	First line PFS

End point description:

The first line PFS was defined as the progression free survival interval during first line treatment. Patients without progression at the last tumor assessment date during their study participation were censored at this last tumor assessment date (exception: availability of validated information about a later onset of progression or a longer progression free interval – in such a case the date of the follow-up assessment was either defined as the onset of progression or replaced the last tumor assessment date). Missing onset of progression data because of refusal or because of death was replaced. If several response evaluations for a patient showed progressive disease (PD), the time to PD was assessed by using the first of these measurements.

End point type	Secondary

End point timeframe:

From start until end of 1st-line treatment

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	62		
Units: Days				
median (confidence interval 95%)	241.000 (203.841 to 278.159)	280.000 (233.398 to 326.602)		

Attachments (see zip file)	Secondary Endpoint 1st-line PFS/2 Secondary Endpoint_First

Statistical analyses

Statistical analysis title	Efficacy analysis first-line PFS

Statistical analysis description:

Survival functions were calculated by the Kaplan-Meier estimator and compared by using the Mantel-Haenszel-Log-Rank-Test.
For variables representing a proportion of patients achieving a given clinical endpoint, cumulative incidences over time were estimated by the Kaplan-Meier method.

Comparison groups	Arm A v Arm B
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.474
Method	Mantel-Haenszel

Secondary: Second-Line PFS

End point title	Second-Line PFS

End point description:

The second line PFS was defined as the progression free survival interval during second line treatment. Patients without progression at the last tumor assessment date during their study participation were censored at this last tumor assessment date (exception: availability of validated information about a later onset of progression or a longer progression free interval – in such a case the date of the follow-up assessment was either defined as the onset of progression or replaced the last tumor assessment date). Missing onset of progression data because of refusal or because of death was replaced.
If several response evaluations for a patient showed progressive disease (PD), the time to PD was assessed by using the first of these measurements.

End point type	Secondary

End point timeframe:

Start of 2nd-line treatment until progression

End point values	Arm A (1st- and 2nd-line treatment)	Arm B (1st- and 2nd-line treatment)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	32	24		
Units: Days				
median (confidence interval 95%)	129.000 (60.340 to 197.660)	155.000 (108.190 to 201.810)		

Attachments (see zip file)	Secondary Endpoint 2nd-line PFS/3 Secondary

Statistical analyses

Statistical analysis title	Efficacy analysis second-line PFS

Statistical analysis description:

Survival functions were calculated by the Kaplan-Meier estimator and compared by using the Mantel-Haenszel-Log-Rank-Test.
For variables representing a proportion of patients achieving a given clinical endpoint, cumulative incidences over time were estimated by the Kaplan-Meier method.

Comparison groups	Arm A (1st- and 2nd-line treatment) v Arm B (1st- and 2nd-line treatment)
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.464
Method	Mantel-Haenszel

Secondary: Overall response rate

End point title	Overall response rate

End point description:

The rate of overall response was measured as the response rate from randomization until the day of documented complete response (CR) or partial response (PR) (whichever status is recorded first).

End point type	Secondary

End point timeframe:

Start of 1st-line treatment until end of 2nd-line treatment

End point values	Arm A (1st- and 2nd-line treatment)	Arm B (1st- and 2nd-line treatment)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	58	62		
Units: number				
Event	32	36		
No Event	26	26		

Attachments (see zip file)	Secondary Endpoint Overall response rate/4 Secondary

Statistical analyses

Statistical analysis title	Efficacy analysis overall response rate

Statistical analysis description:

For categorical data the Fisher’s Exact Test (2 x 2 tables) or the generalization of the Fisher’s Exact test for n x m tables were used.

Comparison groups	Arm A (1st- and 2nd-line treatment) v Arm B (1st- and 2nd-line treatment)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.854
Method	Fisher exact

Secondary: Time to response

End point title	Time to response

End point description:

Time to overall response was measured from the time of randomization until the day of documented complete response (CR) or partial response (PR) (whichever status is recorded first). Patients without response were censored at the date of the last tumor assessment, the date of death or the date of refusal.

End point type	Secondary

End point timeframe:

From start of 1st-line treatment until end of 2nd-line treatment

End point values	Arm A (1st- and 2nd-line treatment)	Arm B (1st- and 2nd-line treatment)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	58	62		
Units: Days				
median (confidence interval 95%)	185.000 (97.423 to 272.577)	178.000 (127.949 to 228.051)		

Attachments (see zip file)	Secondary Endpoint Time to response/5 Secondary

Statistical analyses

Statistical analysis title	Efficacy analysis time to response

Statistical analysis description:

Survival functions were calculated by the Kaplan-Meier estimator and compared by using the Mantel-Haenszel-Log-Rank-Test.
For variables representing a proportion of patients achieving a given clinical endpoint, cumulative incidences over time were estimated by the Kaplan-Meier method.

Comparison groups	Arm A (1st- and 2nd-line treatment) v Arm B (1st- and 2nd-line treatment)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.728
Method	Mantel-Haenszel

Secondary: Duration of response

End point title	Duration of response

End point description:

Duration of overall response was measured from the time that measurement criteria are met for complete response (CR) or partial response (PR) (whichever status was recorded first) until the onset of progression. Patients without progression at the last tumor assessment date during their study participation were censored at this last tumor assessment date (exception: availability of validated information about a later onset of progression or a longer progression free interval – in such a case the date of the follow-up assessment was either defined as the onset of progression or replaced the last tumor assessment date).
Missing onset of progression data because of refusal or because of death was replaced.
If several response evaluations for a patient showed progressive disease (PD), the time to PD was assessed by using the first of these measurements.

End point type	Secondary

End point timeframe:

From 1st-line treatment until end of 2nd-line treatment

End point values	Arm A (1st- and 2nd-line treatment)	Arm B (1st- and 2nd-line treatment)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	32	36		
Units: Days				
median (confidence interval 95%)	244.000 (166.888 to 321.112)	315.000 (142.297 to 487.703)		

Attachments (see zip file)	Secondary Endpoint Duration of response/6 Secondary

Statistical analyses

Statistical analysis title	Efficacy analysis duration of response

Statistical analysis description:

Survival functions were calculated by the Kaplan-Meier estimator and compared by using the Mantel-Haenszel-Log-Rank-Test.
For variables representing a proportion of patients achieving a given clinical endpoint, cumulative incidences over time were estimated by the Kaplan-Meier method.

Comparison groups	Arm A (1st- and 2nd-line treatment) v Arm B (1st- and 2nd-line treatment)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.668
Method	Mantel-Haenszel

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall survival was measured as the time from the randomization date to the date of death. Patients without death date were censored at the date of the last tumor assessment (exception: availability of validated information about a later exitus date or a prolonged survival – in such a case the date of the follow-up assessment was either defined as the exitus date or replaced the last tumor assessment date) or the date of refusal.

End point type	Secondary

End point timeframe:

From 1st-line treatment until end of follow-up period

End point values	Arm A (1st- and 2nd-line treatment)	Arm B (1st- and 2nd-line treatment)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	58	62		
Units: Days				
median (confidence interval 95%)	593.000 (506.691 to 679.309)	643.000 (437.227 to 848.773)		

Attachments (see zip file)	Secondary Endpoint Overall survival/7_Secondary

Statistical analyses

Statistical analysis title	Efficacy analysis overall survival

Statistical analysis description:

Survival functions were calculated by the Kaplan-Meier estimator and compared by using the Mantel-Haenszel-Log-Rank-Test.
For variables representing a proportion of patients achieving a given clinical endpoint, cumulative incidences over time were estimated by the Kaplan-Meier method.

Comparison groups	Arm A (1st- and 2nd-line treatment) v Arm B (1st- and 2nd-line treatment)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.618
Method	Mantel-Haenszel

Secondary: Best response 1st-Line

End point title	Best response 1st-Line

End point description:

Best response in first line was based on the tumor assessments (based on RECIST criteria) using CT scans, MRI scans, X-ray, bone scan and clinical examination.

End point type	Secondary

End point timeframe:

From start of 1st-line treatment until end of 1st-line treatment

End point values	Arm A (1st- and 2nd-line treatment)	Arm B (1st- and 2nd-line treatment)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	53	54		
Units: number				
Progressive Disease (PD)	4	1		
Stable Disease (SD)	21	23		
Partial Response (PR)	26	30		
Complete Response (CR)	2	0		

Attachments (see zip file)	Secondary Endpoint Best response 1st-line/8 Secondary

Statistical analyses

Statistical analysis title	Efficacy Analysis Best Response 1st line

Statistical analysis description:

For ordinal data the exact Mann-Whitney-U-Test was used.

Comparison groups	Arm A (1st- and 2nd-line treatment) v Arm B (1st- and 2nd-line treatment)
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.792
Method	exact Mann-Whitney-U test

Secondary: Best response 2nd-line

End point title	Best response 2nd-line

End point description:

Best response in second line was based on the tumor assessments (based on RECIST criteria) using CT scans, MRI scans, X-ray, bone scan and clinical examination.

End point type	Secondary

End point timeframe:

From start of 2nd-line treatment until progression during 2nd-line treatment or follow-up

End point values	Arm A (1st- and 2nd-line treatment)	Arm B (1st- and 2nd-line treatment)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	23		
Units: number				
Progressive Disease (PD)	7	8		
Stable Disease (SD)	11	13		
Partial Response (PR)	6	2		
Complete Response (CR)	0	0		

Attachments (see zip file)	Secondary Endpoint Best response 2nd-line/9 Secondary

Statistical analyses

Statistical analysis title	Efficacy analysis best response 2nd-line

Statistical analysis description:

For ordinal data the exact Mann-Whitney-U-Test was used.

Comparison groups	Arm A (1st- and 2nd-line treatment) v Arm B (1st- and 2nd-line treatment)
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.371
Method	exact Mann-Whitney-U test

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From enrollment until 28 days of last study treatment for the individual patient.
Adverse events/serious adverse events were collected until last patient last visit (31-Aug-2017); database snapshot was done after data cleaning (28-Nov-2018).

Adverse event reporting additional description:

Clarification regarding threshold for reporting non-serious adverse events: if more than 5 % of patients within on reporting group were affected, non-serious adverse event was reported (more than 3 patients within Arm A and/or Arm B).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Arm A

Reporting group description:

1st-line treatment with XELIRI+Bevacizumab for 6 months (8 cycles): capecitabine : 800mg/m2 bid d1-14, bevacizumab 7,5 mg/kg given on day 1 q3w combined with irinotecan 200mg/m2 iv. d 1 q3w followed by maintenance treatment until progression: bevacizumab (7.5 mg/kg q3w) ± capecitabine (1000 mg/m2 bid, days 1-14 q3w); in case of progression followed by 2nd-line treatment XELOX+Bevacizumab for 4 months (6 cycles).

Reporting group title	Arm B

Reporting group description:

1st-line treatment with XELOX+Bevacizumab for 6 months (8 cycles): capecitabine 1000mg/m2 bid d1-14, bevacizumab 7,5 mg/kg given on d1 q3w combined with oxaliplatin 130mg/m2 iv. d 1 q3w followed by maintenance treatment until progression: bevacizumab (7.5 mg/kg q3w) ± capecitabine (1000 mg/m2 bid, days 1-14 q3w); in case of progression followed by 2nd-line treatment XELIRI+Bevacizumab for 4 months (6 cycles)

Serious adverse events	Arm A	Arm B	
Total subjects affected by serious adverse events			
subjects affected / exposed	43 / 58 (74.14%)	51 / 62 (82.26%)	
number of deaths (all causes)	4	8	
number of deaths resulting from adverse events	3	7	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Laryngeal cancer			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to abdominal wall			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 58 (1.72%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Colectomy	Additional description: Curative surgery for residual primary tumor of metastatic colorectal cancer (mCRC)		
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colostomy	Additional description: Curative surgery for residual primary tumor of metastatic colorectal cancer (mCRC)		
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatectomy	Additional description: Unplanned curative surgery of hepatic metastases of colorectal cancer (mCRC)		
subjects affected / exposed	6 / 58 (10.34%)	8 / 62 (12.90%)	
occurrences causally related to treatment / all	0 / 6	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung lobectomy	Additional description: Unplanned curative surgery of lung metastases of colorectal cancer (mCRC)		

subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctectomy	Additional description: Curative surgery for residual primary tumor of metastatic colorectal cancer (mCRC)		
subjects affected / exposed	2 / 58 (3.45%)	2 / 62 (3.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctocolectomy	Additional description: Curative surgery for residual primary tumor of metastatic colorectal cancer (mCRC)		
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary resection	Additional description: Unplanned curative surgery of lung metastases of colorectal cancer (mCRC)		
subjects affected / exposed	2 / 58 (3.45%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salpingo-oophorectomy bilateral	Additional description: Surgery of metastasis of colorectal cancer		
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sigmoidectomy	Additional description: Curative surgery for residual primary tumor of metastatic colorectal cancer (mCRC)		
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal ablation	Additional description: Unplanned curative surgery of lung metastases of colorectal cancer (mCRC)		
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

General physical health deterioration			
subjects affected / exposed	2 / 58 (3.45%)	5 / 62 (8.06%)	
occurrences causally related to treatment / all	0 / 2	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 58 (1.72%)	4 / 62 (6.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcer			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergic reaction			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hiccups			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal pain			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 58 (1.72%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	6 / 58 (10.34%)	8 / 62 (12.90%)	
occurrences causally related to treatment / all	7 / 7	6 / 8	
deaths causally related to treatment / all	0 / 0	0 / 2	
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Confusional state			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic attack			

subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Body temperature increased			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight increased			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Gastrointestinal stoma necrosis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Scapula fracture			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma site inflammation			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Intestinal atresia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 58 (1.72%)	2 / 62 (3.23%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Haemorrhage intracranial			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiplegia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Restless legs syndrome			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	3 / 58 (5.17%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic anaemia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 58 (3.45%)	3 / 62 (4.84%)	
occurrences causally related to treatment / all	0 / 2	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 58 (1.72%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Constipation			
subjects affected / exposed	2 / 58 (3.45%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	4 / 58 (6.90%)	5 / 62 (8.06%)	
occurrences causally related to treatment / all	4 / 4	5 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer perforation			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	2 / 58 (3.45%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated inguinal hernia			

subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 58 (0.00%)	3 / 62 (4.84%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 58 (1.72%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal perforation			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Subileus			
subjects affected / exposed	1 / 58 (1.72%)	2 / 62 (3.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	1 / 58 (1.72%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder fistula			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder perforation			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 58 (1.72%)	2 / 62 (3.23%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bursitis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Medical device site infection			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 58 (0.00%)	2 / 62 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal abscess			

subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Sinusitis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestine gangrene			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic infection			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 58 (1.72%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dehydration			
subjects affected / exposed	1 / 58 (1.72%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A	Arm B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 58 (94.83%)	61 / 62 (98.39%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	13 / 58 (22.41%)	14 / 62 (22.58%)	
occurrences (all)	23	19	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	21 / 58 (36.21%)	27 / 62 (43.55%)	
occurrences (all)	43	63	
General physical health deterioration			
subjects affected / exposed	4 / 58 (6.90%)	3 / 62 (4.84%)	
occurrences (all)	6	3	
Mucosal inflammation			
subjects affected / exposed	7 / 58 (12.07%)	6 / 62 (9.68%)	
occurrences (all)	9	9	
Oedema			
subjects affected / exposed	1 / 58 (1.72%)	4 / 62 (6.45%)	
occurrences (all)	1	8	
Pain			
subjects affected / exposed	0 / 58 (0.00%)	4 / 62 (6.45%)	
occurrences (all)	0	4	
Pyrexia			
subjects affected / exposed	3 / 58 (5.17%)	5 / 62 (8.06%)	
occurrences (all)	5	9	
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	5 / 58 (8.62%)	5 / 62 (8.06%)	
occurrences (all)	5	5	
Dyspnoea			
subjects affected / exposed	6 / 58 (10.34%)	5 / 62 (8.06%)	
occurrences (all)	7	7	
Epistaxis			

subjects affected / exposed	1 / 58 (1.72%)	6 / 62 (9.68%)	
occurrences (all)	1	7	
Psychiatric disorders			
Depression			
subjects affected / exposed	3 / 58 (5.17%)	4 / 62 (6.45%)	
occurrences (all)	3	11	
Insomnia			
subjects affected / exposed	5 / 58 (8.62%)	3 / 62 (4.84%)	
occurrences (all)	7	3	
Investigations			
Blood pressure increased			
subjects affected / exposed	3 / 58 (5.17%)	3 / 62 (4.84%)	
occurrences (all)	4	5	
Body temperature increased			
subjects affected / exposed	1 / 58 (1.72%)	4 / 62 (6.45%)	
occurrences (all)	1	4	
C-reactive protein increased			
subjects affected / exposed	4 / 58 (6.90%)	10 / 62 (16.13%)	
occurrences (all)	5	15	
Weight decreased			
subjects affected / exposed	7 / 58 (12.07%)	14 / 62 (22.58%)	
occurrences (all)	7	19	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	6 / 58 (10.34%)	7 / 62 (11.29%)	
occurrences (all)	8	9	
Headache			
subjects affected / exposed	7 / 58 (12.07%)	1 / 62 (1.61%)	
occurrences (all)	8	2	
Neuropathy peripheral			
subjects affected / exposed	6 / 58 (10.34%)	4 / 62 (6.45%)	
occurrences (all)	7	4	
Paraesthesia			
subjects affected / exposed	5 / 58 (8.62%)	7 / 62 (11.29%)	
occurrences (all)	9	10	
Polyneuropathy			

subjects affected / exposed	21 / 58 (36.21%)	37 / 62 (59.68%)	
occurrences (all)	32	90	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 58 (13.79%)	7 / 62 (11.29%)	
occurrences (all)	14	18	
Neutropenia			
subjects affected / exposed	9 / 58 (15.52%)	5 / 62 (8.06%)	
occurrences (all)	22	8	
Thrombocytopenia			
subjects affected / exposed	10 / 58 (17.24%)	3 / 62 (4.84%)	
occurrences (all)	15	3	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	8 / 58 (13.79%)	11 / 62 (17.74%)	
occurrences (all)	9	16	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	15 / 58 (25.86%)	11 / 62 (17.74%)	
occurrences (all)	21	15	
Abdominal pain upper			
subjects affected / exposed	6 / 58 (10.34%)	5 / 62 (8.06%)	
occurrences (all)	8	10	
Constipation			
subjects affected / exposed	16 / 58 (27.59%)	14 / 62 (22.58%)	
occurrences (all)	27	18	
Diarrhoea			
subjects affected / exposed	32 / 58 (55.17%)	24 / 62 (38.71%)	
occurrences (all)	64	59	
Flatulence			
subjects affected / exposed	2 / 58 (3.45%)	7 / 62 (11.29%)	
occurrences (all)	2	8	
Nausea			
subjects affected / exposed	21 / 58 (36.21%)	13 / 62 (20.97%)	
occurrences (all)	38	37	
Stomatitis			

subjects affected / exposed	3 / 58 (5.17%)	4 / 62 (6.45%)	
occurrences (all)	4	7	
Vomiting			
subjects affected / exposed	5 / 58 (8.62%)	8 / 62 (12.90%)	
occurrences (all)	6	8	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	18 / 58 (31.03%)	5 / 62 (8.06%)	
occurrences (all)	25	5	
Dry skin			
subjects affected / exposed	2 / 58 (3.45%)	7 / 62 (11.29%)	
occurrences (all)	2	11	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	20 / 58 (34.48%)	22 / 62 (35.48%)	
occurrences (all)	46	53	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 58 (5.17%)	3 / 62 (4.84%)	
occurrences (all)	4	4	
Back pain			
subjects affected / exposed	4 / 58 (6.90%)	5 / 62 (8.06%)	
occurrences (all)	4	6	
Pain in extremity			
subjects affected / exposed	5 / 58 (8.62%)	1 / 62 (1.61%)	
occurrences (all)	5	1	
Infections and infestations			
Gastrointestinal infection			
subjects affected / exposed	4 / 58 (6.90%)	0 / 62 (0.00%)	
occurrences (all)	4	0	
Nasopharyngitis			
subjects affected / exposed	5 / 58 (8.62%)	8 / 62 (12.90%)	
occurrences (all)	6	10	
Rhinitis			
subjects affected / exposed	3 / 58 (5.17%)	4 / 62 (6.45%)	
occurrences (all)	3	7	
Urinary tract infection			

subjects affected / exposed	11 / 58 (18.97%)	5 / 62 (8.06%)	
occurrences (all)	13	5	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	15 / 58 (25.86%)	11 / 62 (17.74%)	
occurrences (all)	26	23	
Hypokalaemia			
subjects affected / exposed	5 / 58 (8.62%)	12 / 62 (19.35%)	
occurrences (all)	7	20	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 June 2013	This change was done to clarify that first-line treatment of 6 months is corresponding with 8 cycles of chemotherapy and second-line treatment of 4 months is corresponding with 6 cycles of chemotherapy. All patients should receive the same number of cycles if tolerated. Furthermore advice was given in case of not previously done resection of colorectal tumor or if subjects become resectable regarding tumor metastases. In case of surgery of primary colorectal tumor or resection of metastases bevacizumab treatment should be interrupted 6 to 8 weeks prior to planned surgery and restarted 4 weeks after surgery. Chemotherapy treatment with oxaliplatin, irinotecan and/or capecitabine should be interrupted at least 4 weeks prior to surgery and restarted 4 weeks after surgery. Interruption of protocol treatment due to surgery of primary colorectal tumor or metastases will not result in withdrawal of subjects or change of protocol treatment dosing.
10 December 2015	Recruitment period was longer than expected (33 instead of 24 months expected) and successful treatment of patients within the different phases of the study is also longer than expected. Therefore, duration of study has to be adapted.

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.

not applicable

Notes: