



Clinical trial results:

FOLFOX/bevacizumab with or without irinotecan in first-line treatment for metastatic colorectal cancer. A randomized phase II study.

Summary

EudraCT number	2010-022162-27
Trial protocol	DE
Global end of trial date	31 August 2018

Results information

Result version number	v1 (current)
This version publication date	21 May 2021
First version publication date	21 May 2021
Summary attachment (see zip file)	Final Study Report (FSR_CHARTA-V01F_2019-08-30.pdf)

Trial information

Trial identification

Sponsor protocol code	AIO0209
-----------------------	---------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01321957
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Martin-Luther-Universität Halle-Wittenberg
Sponsor organisation address	Magdeburger Str. 8, Halle (Saale), Germany, 06112
Public contact	Koordinierungszentrum für klinische Studien Halle/S., Koordinierungszentrum für klinische Studien Halle/S., +49 3455574903, aio0209@kks-halle.de
Scientific contact	Koordinierungszentrum für klinische Studien Halle/S., Koordinierungszentrum für klinische Studien Halle/S., +49 3455574903, aio0209@kks-halle.de

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	28 March 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	31 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy of 5-Fluorouracil (5-FU), oxaliplatin and irinotecan (FOLFOXIRI-Regimen) with bevacizumab versus 5-FU and oxaliplatin (FOLFOX-Regimen) with bevacizumab in patients with metastatic colorectal cancer.

Secondary objectives were safety and tolerability of the treatment as well as the progression free survival, overall survival, secondary resection rate, quality of life and the prognostic value of and the allocation to the clinical classification of patients. The addition of irinotecan might be more effective in terms of response and survival in bevacizumab insensitive compared to bevacizumab sensitive patients, therefore potential markers (VEGF-A, osteopontin, G-CSF, Ang-2, sVEGFR2, neuropilin, DII4, CAIX/HIF1a, etc.) were evaluated.

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards consistent with Good Clinical Practice and applicable regulations. The responsible investigator ensured that this study was conducted in agreement with either the Declaration of Helsinki (from June 1964, Tokyo October 1975, Venice October 1983, Hong Kong September 1989, Somerset West October 1996 and Edinburgh amendments from 2000) or the laws and regulations. The protocol has been written, and the study has been conducted according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice (reference: <http://www.ifpma.org/pdfifpma/e6.pdf>). The protocol was approved by Independent Ethics Committees.

Background therapy:

Prevention of nausea/vomiting: NK1 receptor antagonist, 5-HT3 antagonists and dexamethasone were recommended for oxaliplatin-based CT.

Delayed nausea/vomiting: oral dexamethasone; metoclopramide, alizapride, prochlorperazine at the discretion of the physician. Subjects had a supply of antiemetics available at home. Oral metoclopramide was recommended for capecitabine-induced nausea (5-HT3 antagonists at the discretion of the investigator).

Diarrhoea and neutropenia: empiric use of antibiotics as prophylaxis against bowel sepsis was to be considered. Use of a quinolone was suggested.

Anticoagulation: full dose anticoagulants as long as the INR or aPTT was within therapeutic limits and the patient had been on a stable dose for anticoagulants for at least two weeks at the time of registration. Monitoring of INR for oral anticoagulants was recommended.

Antivirals and Antiprotozoals: Capecitabine should not be administered together with the halogenated antiviral drug sorivudine or its chemically related analogues. Caution in case of administration of metronidazole.

Gastrointestinal Drugs: Care needed to be taken if a subject was taking both capecitabine and cimetidine.

Allopurinol: Concomitant use of allopurinol with capecitabine and 5-FU should be avoided.

Anti-epileptic Substances: Subjects taking phenytoin concomitantly with capecitabine had to be regularly monitored for increased phenytoin plasma concentrations and associated clinical symptoms.

Growth factors: Haematopoietic growth factors (i.e., G- or GM-CSF) was used according to institutional guidelines to treat febrile neutropenia.

Evidence for comparator:

Usually, bevacizumab and 5-FU are combined with either oxaliplatin or irinotecan. The chemotherapy regimen selected for this study (FOLFOX) was chosen on the basis of the higher response rates and survival durations as compared with other fluoropyrimidine-based regimens, and thus represent appropriate regimens for combination with bevacizumab. This therapy is therefore being used as a standard of care first-line therapy.

Actual start date of recruitment	28 July 2011
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	Germany: 250
Worldwide total number of subjects	250
EEA total number of subjects	250

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)	161
From 65 to 84 years	89
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between July 28, 2011 and September 23, 2014, 250 patients were enrolled at 50 trial sites in Germany. The last patient finished the maintenance treatment in August 2017. Follow-up (LPV) was finished in August 2018.

Pre-assignment

Screening details:

All patients with metastatic colorectal carcinoma presenting at the participating trial sites with an indication for therapy were screened for inclusion/ exclusion criteria for this trial. All patients who met the inclusion/ exclusion criteria were offered participation in the study. There was no selection based on other criteria.

Period 1

Period 1 title	CHARTA overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	FOLFOX+beva

Arm description:

Induction chemotherapy: FOLFOX (oxaliplatin, LV and 5-FU and bevacizumab, biweekly), until progression, intolerable toxicity, and secondary resection or for a max. of 12 cycles (6 months). Maintenance therapy: either 5-FU/LV and bevacizumab (biweekly) or capecitabine and bevacizumab (5-FU or capecitabine at the investigators discretion) for up to 12 months until progression or intolerable toxicity. Maximum treatment duration: 18 months (6 months of FOLFOX and bevacizumab and 12 months of maintenance). In case of secondary resection treatment had to be resumed 4–8 weeks postoperatively for a total of 6 months FOLFOX and bevacizumab (pre- and post-op treatment), followed by maintenance treatment for total treatment duration of up to 12 months in the absence of progression or intolerable toxicity.

Arm type	Active comparator
Investigational medicinal product name	5-Fluoruracil
Investigational medicinal product code	5-FU
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

3200 mg/sqm i.v. over 48 hours at day 1-3 of each cycle for a maximum of 12 cycles (6 months) in the induction therapy and another 12 months in the maintenance therapy. Maximal treatment duration is 18 months.

Investigational medicinal product name	Leucovorin
Investigational medicinal product code	I-LV
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg/sqm i.v. over two hours at day 1 of each cycle for a maximum of 12 cycles (6 months) in the induction therapy and another 12 months in the maintenance therapy. Maximal treatment duration is 18 months.

Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
85 mg/sqm i.v. over two hours at day 1 of each cycle for a maximum of 12 cycles (6 months) in the induction therapy	
Investigational medicinal product name	Avastin
Investigational medicinal product code	bevacizumab
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
5 mg/kg i.v. over 30 to 90 min at day 1 of each cycle for a maximum of 12 cycles (6 months) in the induction therapy.	
Investigational medicinal product name	Xeloda
Investigational medicinal product code	Capecitabine
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
1600 mg/sqm per day on day 1–14, every three weeks in the maintenance therapy (maximum for 12 months)	
Arm title	FOLFOXIRI+beva
Arm description:	
Induction chemotherapy: FOLFOXIRI (oxaliplatin, LV and 5-FU and bevacizumab + irinotecan, biweekly), until progression, intolerable toxicity, and secondary resection or for a max. of 12 cycles (6 months). Maintenance therapy: either 5-FU/LV and bevacizumab (biweekly) or capecitabine and bevacizumab (5-FU or capecitabine at the investigators discretion) for up to 12 months until progression or intolerable toxicity. Maximum treatment duration: 18 months (6 months of FOLFOX and bevacizumab + irinotecan + 12 M of maintenance). In case of secondary resection treatment had to be resumed 4–8 weeks postoperatively for a total of 6 months FOLFOX and bevacizumab + irinotecan (pre- and post-op treatment), followed by maintenance treatment for total treatment duration of up to 12 months in the absence of progression or intolerable toxicity.	
Arm type	Experimental
Investigational medicinal product name	5-Fluoruracil
Investigational medicinal product code	5-FU
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
3200 mg/sqm i.v. over 48 hours at day 1–3 of each cycle for a maximum of 12 cycles (6 months) in the induction therapy and another 12 months in the maintenance therapy. Maximal treatment duration is 18 months.	
For the first cycle in the FOLFOXIRI+beva arm a dose reduction of 5-FU/LV to 75% was possible for patients who had an increased risk for severe toxicity as judged by the treating physician. If no significant toxicity occurs (e.g. diarrhea grade 3), treatment had to be continued with full dose. Upfront dose reduction and reescalation was at the discretion of the investigator.	
Investigational medicinal product name	Leucovorin
Investigational medicinal product code	I-LV
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
200 mg/sqm i.v. over two hours at day 1 of each cycle for a maximum of 12 cycles (6 months) in the induction therapy and another 12 months in the maintenance therapy. Maximal treatment duration is 18 months.	

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

Dosage and administration details:

85 mg/sqm i.v. over two hours at day 1 of each cycle for a maximum of 12 cycles (6 months) in the induction therapy

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

Dosage and administration details:

5 mg/kg i.v. over 30 to 90 min at day 1 of each cycle for a maximum of 12 cycles (6 months) in the induction therapy.

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

Dosage and administration details:

1600 mg/sqm per day on day 1–14, every three weeks in the maintenance therapy (maximum for 12 months)

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

Dosage and administration details:

165 mg/sqm i.v. over two hours on day 1 of each cycle for a maximum of 12 cycles (6 months) in the induction therapy.

For the first cycle in the FOLFOXIRI+beva arm a dose reduction of irinotecan to 75% was possible for patients who had an increased risk for severe toxicity as judged by the treating physician. If no significant toxicity occurs (e.g. diarrhea grade 3), treatment had to be continued with full dose. Upfront dose reduction and reescalation was at the discretion of the investigator.

Number of subjects in period 1	FOLFOX+beva	FOLFOXIRI+beva
Started	126	124
Completed	121	121
Not completed	5	3
Consent withdrawn by subject	3	1
Histologic diagnosis of neuroendocrine tumor	1	1
Randomisation failure - CTx before randomisation	1	-
Protocol deviation	-	1

Baseline characteristics

Reporting groups

Reporting group title	FOLFOX+beva
-----------------------	-------------

Reporting group description:

Induction chemotherapy: FOLFOX (oxaliplatin, LV and 5-FU and bevacizumab, biweekly), until progression, intolerable toxicity, and secondary resection or for a max. of 12 cycles (6 months). Maintenance therapy: either 5-FU/LV and bevacizumab (biweekly) or capecitabine and bevacizumab (5-FU or capecitabine at the investigators discretion) for up to 12 months until progression or intolerable toxicity. Maximum treatment duration: 18 months (6 months of FOLFOX and bevacizumab and 12 months of maintenance). In case of secondary resection treatment had to be resumed 4–8 weeks postoperatively for a total of 6 months FOLFOX and bevacizumab (pre- and post-op treatment), followed by maintenance treatment for total treatment duration of up to 12 months in the absence of progression or intolerable toxicity.

Reporting group title	FOLFOXIRI+beva
-----------------------	----------------

Reporting group description:

Induction chemotherapy: FOLFOXIRI (oxaliplatin, LV and 5-FU and bevacizumab + irinotecan, biweekly), until progression, intolerable toxicity, and secondary resection or for a max. of 12 cycles (6 months). Maintenance therapy: either 5-FU/LV and bevacizumab (biweekly) or capecitabine and bevacizumab (5-FU or capecitabine at the investigators discretion) for up to 12 months until progression or intolerable toxicity. Maximum treatment duration: 18 months (6 months of FOLFOX and bevacizumab + irinotecan + 12 M of maintenance). In case of secondary resection treatment had to be resumed 4–8 weeks postoperatively for a total of 6 months FOLFOX and bevacizumab + irinotecan (pre- and post-op treatment), followed by maintenance treatment for total treatment duration of up to 12 months in the absence of progression or intolerable toxicity.

Reporting group values	FOLFOX+beva	FOLFOXIRI+beva	Total
Number of subjects	126	124	250
Age categorical			
Subjects not completed the trial were excluded from analysis - Not determined.			
Units: Subjects			
<= 30 year	2	0	2
31-40 years	8	5	13
41-50 years	14	17	31
51-60 years	32	40	72
61-70 years	44	40	84
71-80 years	21	18	39
> 80 years	0	1	1
Not determined (excl.)	5	3	8
Age continuous			
Subjects not completed the trial (see Subject disposition) were excluded from analysis. Arm FOLFOX+beva: n=121, excluded 5 Arm FOLFOXIRI+beva: n=121, excluded 3			
Units: years			
arithmetic mean	60	59.5	
standard deviation	± 11.4	± 9.9	-
Gender categorical			
Subjects not completed the trial (see Subject disposition) were excluded from analysis - Not determined.			
Units: Subjects			
Female	42	43	85
Male	79	78	157
Not determined	5	3	8

ESMO clinical group - stratum			
group 1: liver and/or lung metastasis potentially resectable after downsizing, comorbidity allowing surgery group 2: multiple metastasis, rapid progression, risk of rapid deterioration, unlikely to become resectablepage group 3: not resectable and no symptoms or risk of deterioration *not determined for excluded subjects (see subject disposition)			
Units: Subjects			
group 1	35	35	70
group 2	67	67	134
group 3	19	19	38
not determined	5	3	8
ECOG performance status			
Units: Subjects			
ECOG 0	56	62	118
ECOG 1	56	52	108
ECOG 2	6	3	9
not determined	8	7	15
BMI - categories acc. to WHO			
Units: Subjects			
< 18.5	2	4	6
18.5 - < 25	55	50	105
25 - < 30	43	44	87
30 - < 35	14	17	31
35 - < 40	2	3	5
>= 40	4	3	7
not determined	6	3	9
BRAF mutation			
Units: Subjects			
wildtype	91	85	176
mutated	5	8	13
not done	30	31	61
all-RAS mutation, any exon			
Units: Subjects			
no mutation	47	53	100
mutation	59	61	120
not determined	20	10	30
Grading			
Units: Subjects			
G1	6	4	10
G2	70	73	143
G3	30	33	63
G4	0	1	1
Gx	12	10	22
not determined	8	3	11
Location of primary tumor			
Units: Subjects			
Colon	60	69	129
Rectum	36	33	69
Rectum and Colon	21	18	39
not determined	9	4	13
Tumor sidedness : left vs. right			

Units: Subjects			
left colon or rectum	88	84	172
right colon	28	36	64
not determined	10	4	14
Stage of primary tumor			
at first diagnosis			
Units: Subjects			
0.	2	0	2
I.	0	2	2
IIA	4	3	7
IIB	3	0	3
IIIA	2	1	3
IIIB	1	5	6
IIIC	3	6	9
IV	97	94	191
not determined	14	13	27
TNM stage - T status			
Units: Subjects			
T1	1	0	1
T2	9	4	13
T3	48	62	110
T4	38	32	70
Tis	0	0	0
Tx	20	17	37
not determined	10	9	19
TNM stage - N status			
Units: Subjects			
N0	27	15	42
N1	41	38	79
N2	34	38	72
N3	0	3	3
Nx	18	22	40
not determined	6	8	14
TNM stage - M status			
Units: Subjects			
M0	8	8	16
M1	107	108	215
Mx	4	4	8
not determined	7	4	11
Köhne Score			
Units: Subjects			
low risk	11	9	20
intermediate risk	85	85	170
high risk	20	18	38
not determined	10	12	22
Induction therapy: Max. number of cycles per patient			
Units: Subjects			
1 Cycle/n	1	4	5
2 Cycle/n	2	5	7
3 Cycle/n	4	4	8
4 Cycle/n	7	9	16

5 Cycle/n	12	5	17
6 Cycle/n	6	3	9
7 Cycle/n	1	2	3
8 Cycle/n	9	5	14
9 Cycle/n	4	4	8
10 Cycle/n	2	3	5
11 Cycle/n	9	5	14
12 Cycle/n	61	72	133
not determined	8	3	11
Maintenance therapy: Number of treatment cycles - by categories			
FOLFOX+beva: n=58 FOLFOXIRI+beva: n=66			
Units: Subjects			
up to 6 cycles	24	26	50
up to 12 cycles	14	16	30
up to 18 cycles	11	9	20
up to 24 cycles	7	13	20
> 24 cycles	2	2	4
not received maintenance therapy	63	55	118
not determined	5	3	8
Height			
FOLFOX+beva: n=120 FOLFOXIRI+beva: n=121			
Units: cm			
arithmetic mean	172.9	171.9	
standard deviation	± 9.1	± 9.0	-
Weight			
FOLFOX+beva: n=120 FOLFOXIRI+beva: n=121			
Units: kg			
arithmetic mean	78.5	77.5	
standard deviation	± 18.6	± 15.9	-
Body mass index (BMI)			
FOLFOX+beva: n=120 FOLFOXIRI+beva: n=121			
Units: Index			
arithmetic mean	26.2	26.2	
standard deviation	± 5.5	± 5.2	-
Duration of therapy			
Units: days			
arithmetic mean	147.8	155.6	
standard deviation	± 63.3	± 68.6	-
Duration of induction therapy			
Units: Days			
median	168	168	
full range (min-max)	14 to 392	14 to 307	-
Induction therapy: Dose intensity in % of calculated full dose - fluoropyrimidin			
FOLFOX+beva: n=119 FOLFOXIRI+beva: n=121			
Units: [%]			
median	97.9	94.8	
full range (min-max)	52.8 to 112.5	53.3 to 106.3	-

Induction therapy: Dose intensity in % of calculated full dose - oxaliplatin			
FOLFOX+beva: n=120 FOLFOXIRI+beva: n=121			
Units: [%] median full range (min-max)	97.7 51.9 to 107.8	93.9 24.7 to 105.8	-
Induction therapy: Dose intensity in % of calculated full dose - bevacizumab			
FOLFOX+beva: n=120 FOLFOXIRI+beva: n=121			
Units: [%] median full range (min-max)	98.9 0 to 141.7	96.9 0 to 115.5	-
Induction therapy: Dose intensity in % of calculated full dose - leucovorin			
FOLFOX+beva: n=120 FOLFOXIRI+beva: n=121			
Units: [%] median full range (min-max)	99.4 40 to 216.5	97.1 54.2 to 194.8	-
Induction therapy: Dose intensity in % of calculated full dose - irinotecan			
FOLFOX+beva: n=0 FOLFOXIRI+beva: n=121			
Units: [%] median full range (min-max)	0 0 to 0	92.7 13 to 105.7	-
Induction therapy: Mean dose intensity over 3* (arm A) or 4* (arm B) substances			
FOLFOX+beva (arm A): n=120 -- *5-FU/Lv, Oxaliplatin, Bevacizumab FOLFOXIRI+beva (arm B): n=121 -- *5-FU/Lv, Oxaliplatin, Bevacizumab, Irinotecan			
Units: [%] median full range (min-max)	95.6 63.2 to 107.1	90.7 46.1 to 108.3	-
Maintenance therapy: Number of treatment cycles			
FOLFOX+beva: n=58 FOLFOXIRI+beva: n=66			
Units: [n] median full range (min-max)	8 1 to 26	8 1 to 26	-
Maintenance therapy: Duration			
FOLFOX+beva: n=58 FOLFOXIRI+beva: n=66			
Units: weeks median full range (min-max)	21.4 0.3 to 53.1	22.6 0.3 to 75.1	-

End points

End points reporting groups

Reporting group title	FOLFOX+beva
-----------------------	-------------

Reporting group description:

Induction chemotherapy: FOLFOX (oxaliplatin, LV and 5-FU and bevacizumab, biweekly), until progression, intolerable toxicity, and secondary resection or for a max. of 12 cycles (6 months). Maintenance therapy: either 5-FU/LV and bevacizumab (biweekly) or capecitabine and bevacizumab (5-FU or capecitabine at the investigators discretion) for up to 12 months until progression or intolerable toxicity. Maximum treatment duration: 18 months (6 months of FOLFOX and bevacizumab and 12 months of maintenance). In case of secondary resection treatment had to be resumed 4–8 weeks postoperatively for a total of 6 months FOLFOX and bevacizumab (pre- and post-op treatment), followed by maintenance treatment for total treatment duration of up to 12 months in the absence of progression or intolerable toxicity.

Reporting group title	FOLFOXIRI+beva
-----------------------	----------------

Reporting group description:

Induction chemotherapy: FOLFOXIRI (oxaliplatin, LV and 5-FU and bevacizumab + irinotecan, biweekly), until progression, intolerable toxicity, and secondary resection or for a max. of 12 cycles (6 months). Maintenance therapy: either 5-FU/LV and bevacizumab (biweekly) or capecitabine and bevacizumab (5-FU or capecitabine at the investigators discretion) for up to 12 months until progression or intolerable toxicity. Maximum treatment duration: 18 months (6 months of FOLFOX and bevacizumab + irinotecan + 12 M of maintenance). In case of secondary resection treatment had to be resumed 4–8 weeks postoperatively for a total of 6 months FOLFOX and bevacizumab + irinotecan (pre- and post-op treatment), followed by maintenance treatment for total treatment duration of up to 12 months in the absence of progression or intolerable toxicity.

Primary: Progression free survival rate at 9 months (absolute)

End point title	Progression free survival rate at 9 months (absolute)
-----------------	---

End point description:

End point type	Primary
----------------	---------

End point timeframe:

9 months after start of study therapy

End point values	FOLFOX+beva	FOLFOXIRI+beva		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	121		
Units: Subjects				
Progression-free at 9 months	68	81		
Progression at 9 months	48	37		
Not assessable	5	3		

Statistical analyses

Statistical analysis title	PFS@9 - stratified logistic regression
----------------------------	--

Statistical analysis description:

The absolute progression rate was compared by different statistical tests, first by applying a logistic

regression method, stratified by the clinical stage of patients at baseline, which was the test method prospectively defined in the protocol.

Comparison groups	FOLFOXIRI+beva v FOLFOX+beva
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.11
Method	Regression, Logistic

Statistical analysis title	PFS@9 - Fisher's exact test
Comparison groups	FOLFOX+beva v FOLFOXIRI+beva
Number of subjects included in analysis	242
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.135
Method	Fisher exact

Statistical analysis title	PFS@9 - Chi ² -Test
Comparison groups	FOLFOX+beva v FOLFOXIRI+beva
Number of subjects included in analysis	242
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.145
Method	Chi-squared

Primary: Progression free survival rate at 9 months (Kaplan-Meier)

End point title	Progression free survival rate at 9 months (Kaplan-Meier)
End point description: The PFS rate at 9 months was also revealed by the Kaplan-Meier-Method. This method takes also the available information for censored patients into account.	
End point type	Primary
End point timeframe: 9 months after start of study therapy	

End point values	FOLFOX+beva	FOLFOXIRI+beva		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	121		
Units: Percentage				
number (confidence interval 95%)	58 (49 to 67)	69 (61 to 78)		

Statistical analyses

Statistical analysis title	PFS@9 - Kaplan-Meier
Comparison groups	FOLFOX+beva v FOLFOXIRI+beva
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.082
Method	Fisher exact

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)
End point description:	
Progression events (according to RECIST assessment)	
End point type	Secondary
End point timeframe:	
From Start of study therapy until end of follow up	

End point values	FOLFOX+beva	FOLFOXIRI+beva		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	121		
Units: Subjects				
progression events	108	112		
censored	13	9		

Attachments (see zip file)	PFS-Kaplan-Meier.JPG
-----------------------------------	----------------------

Statistical analyses

Statistical analysis title	PFS - Hazard ratio, CI and p-value
Comparison groups	FOLFOX+beva v FOLFOXIRI+beva

Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.17
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.08

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
Death events	
End point type	Secondary
End point timeframe:	
from start of study therapy until end of follow up	

End point values	FOLFOX+beva	FOLFOXIRI+beva		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	121		
Units: Subjects				
death events	98	96		
censored	23	25		

Attachments (see zip file)	Overall Survival/OS-Kaplan-Meier.JPG
-----------------------------------	--------------------------------------

Statistical analyses

Statistical analysis title	OS- Hazard ratio, CI and p-value
Comparison groups	FOLFOX+beva v FOLFOXIRI+beva
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.17
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.09

Secondary: Best response to treatment

End point title	Best response to treatment
End point description:	
End point type	Secondary
End point timeframe:	
from start of study treatment until end of follow-up	

End point values	FOLFOX+beva	FOLFOXIRI+beva		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	114		
Units: Subjects				
CR	6	6		
PR	63	73		
SD	29	25		
PD	16	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Best response by categories

End point title	Best response by categories
End point description:	
End point type	Secondary
End point timeframe:	
from start of study treatment until end of follow-up	

End point values	FOLFOX+beva	FOLFOXIRI+beva		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	114		
Units: Subjects				
response (CR+PR)	69	79		
failure (SD+PD)	45	35		

Statistical analyses

Statistical analysis title	Best response - Fisher's exact test
Comparison groups	FOLFOX+beva v FOLFOXIRI+beva
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.21
Method	Fisher exact

Secondary: Resection of primary tumor - before randomization

End point title	Resection of primary tumor - before randomization
End point description:	
End point type	Secondary
End point timeframe:	
before randomization	

End point values	FOLFOX+beva	FOLFOXIRI+beva		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	121		
Units: Subjects				
no resection	65	72		
primary resected	56	49		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary resection of primary tumor - after randomization

End point title	Secondary resection of primary tumor - after randomization
End point description:	

End point type	Secondary
End point timeframe: from randomization until end of follow up	

End point values	FOLFOX+beva	FOLFOXIRI+beva		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	121		
Units: Subjects				
secondary resection	13	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary resection of metastases

End point title	Secondary resection of metastases
End point description:	
End point type	Secondary
End point timeframe: from randomization until end of follow-up	

End point values	FOLFOX+beva	FOLFOXIRI+beva		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	121		
Units: Subjects				
no secondary resection of metastases	95	91		
secondary resection of metastases	25	30		

Statistical analyses

Statistical analysis title	Secondary resection of metastases - Fisher's exact
Comparison groups	FOLFOX+beva v FOLFOXIRI+beva
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.54
Method	Fisher exact

Secondary: Number of sec. metastases resection by patient

End point title	Number of sec. metastases resection by patient
-----------------	--

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

from randomization until end of follow-up

End point values	FOLFOX+beva	FOLFOXIRI+beva		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	30		
Units: Subjects				
1 met. resection	22	20		
2 met. resections	3	8		
> 2 met. resections	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Location of sec. metastases resections

End point title	Location of sec. metastases resections
-----------------	--

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

from randomization until end of follow-up

End point values	FOLFOX+beva	FOLFOXIRI+beva		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	30		
Units: Subjects				
liver	23	29		
lung	2	1		
peritoneum	0	2		
other	3	4		

Statistical analyses

No statistical analyses for this end point

Secondary: EORTC-QLQ C30 - Global health status

End point title	EORTC-QLQ C30 - Global health status
-----------------	--------------------------------------

End point description:

n: Number of subjects with completed questionnaire

FOLFOX+Beva: Baseline n=109, Cycle 5 n=82, Cycle 9 n= 61, MT cycle 1 n=39, End of therapy n=56

FOLFOXIRI+Beva: Baseline n=109, Cycle 5 n=79, Cycle 9 n= 67, MT cycle 1 n=45, End of therapy n=52

End point type	Secondary
----------------	-----------

End point timeframe:

From randomisation until end of therapy

End point values	FOLFOX+beva	FOLFOXIRI+beva		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	109		
Units: Score				
arithmetic mean (standard deviation)				
Baseline	58 (± 22)	54.8 (± 21.5)		
Cycle 5	61.2 (± 21.6)	57 (± 22.3)		
Cycle 9	57 (± 22.5)	62.4 (± 18.9)		
MT cycle 1	62.2 (± 15.3)	60.9 (± 19.8)		
End of Therapy	56 (± 20.5)	56.9 (± 25.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: EORTC-QLQ CIPN20 - Sensory Scale

End point title	EORTC-QLQ CIPN20 - Sensory Scale
-----------------	----------------------------------

End point description:

n: Number of subjects with completed questionnaire

FOLFOX+Beva: Baseline n=105, Cycle 5 n=78, Cycle 9 n= 58, MT cycle 1 n=35, End of therapy n=53

FOLFOXIRI+Beva: Baseline n=101, Cycle 5 n=73, Cycle 9 n= 64, MT cycle 1 n=45, End of therapy n=45

When presenting score level data, the scoring instructions for the CIPN-20 module highly recommends calculation of Cronbach's alpha coefficient as indicator for reliability of the multi-item score levels. That coefficient should preferably be above 0.70 for any given multi-item scale. The values of Cronbach's alpha for each scale for the CHARTA data are: Sensory scale 0.86, Motor scale 0.83, Autonomic scale

0.59. Since Cronbach's alpha for the autonomic scale is less than 0.7 in this study, only the score values for both sensory scale and motor scale are presented.

End point type	Secondary
----------------	-----------

End point timeframe:

from randomization until end of therapy

End point values	FOLFOX+beva	FOLFOXIRI+beva		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	101		
Units: Score				
arithmetic mean (standard deviation)				
Baseline	4.7 (± 8.4)	5.5 (± 10.5)		
Cycle 5	19.1 (± 18.1)	15.8 (± 16)		
Cycle 9	20.6 (± 16.5)	20.4 (± 17.3)		
MT Cycle 1	33.5 (± 21.1)	33.8 (± 21.3)		
End of therapy	29 (± 23.1)	25.3 (± 20.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: EORTC-QLQ CIPN20 - Motor Scale

End point title	EORTC-QLQ CIPN20 - Motor Scale
-----------------	--------------------------------

End point description:

n: Number of subjects with completed questionnaire

FOLFOX+Beva: Baseline n=76, Cycle 5 n=56, Cycle 9 n= 41, MT cycle 1 n=24, End of therapy n=34

FOLFOXIRI+Beva: Baseline n=79, Cycle 5 n=54, Cycle 9 n= 45, MT cycle 1 n=30, End of therapy n=32

End point type	Secondary
----------------	-----------

End point timeframe:

from randomization until end of therapy

End point values	FOLFOX+beva	FOLFOXIRI+beva		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	79		
Units: Score				
arithmetic mean (standard deviation)				
Baseline	4.1 (± 7.5)	3.4 (± 6.3)		
Cycle 5	7.4 (± 12.4)	8.3 (± 12.9)		
Cycle 9	9.5 (± 14.9)	9.3 (± 10.5)		
MT Cycle 1	11.6 (± 12.3)	14.3 (± 13)		
End of therapy	12.9 (± 13.7)	11.5 (± 16.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Response rate - RAS wildtype

End point title	Response rate - RAS wildtype
-----------------	------------------------------

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

from start of study therapy until end of follow-up

End point values	FOLFOX+beva	FOLFOXIRI+beva		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	44		
Units: Subjects				
response	24	30		
failure	17	14		

Statistical analyses

Statistical analysis title	Response rate RAS wildtype - Fisher's exact
----------------------------	---

Comparison groups	FOLFOX+beva v FOLFOXIRI+beva
-------------------	------------------------------

Number of subjects included in analysis	85
---	----

Analysis specification	Pre-specified
------------------------	---------------

Analysis type	superiority
---------------	-------------

P-value	= 0.38
---------	--------

Method	Fisher exact
--------	--------------

Secondary: Response rate - RAS mutated

End point title	Response rate - RAS mutated
-----------------	-----------------------------

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

from start of study treatment until end of follow up

End point values	FOLFOX+beva	FOLFOXIRI+beva		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	57		
Units: Subjects				
response	36	41		
failure	22	16		

Statistical analyses

Statistical analysis title	Response rate RAS mutated - Fisher's exact
Comparison groups	FOLFOX+beva v FOLFOXIRI+beva
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.32
Method	Fisher exact

Secondary: Response rate - BRAF mutated

End point title	Response rate - BRAF mutated
End point description:	
End point type	Secondary
End point timeframe:	
from start of study treatment until end of follow up	

End point values	FOLFOX+beva	FOLFOXIRI+beva		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	6		
Units: Subjects				
response	4	5		
failure	1	1		

Statistical analyses

Statistical analysis title	Response rate BRAF mutated - Fisher's exact
Comparison groups	FOLFOX+beva v FOLFOXIRI+beva

Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact

Secondary: Response rate - Clinical group 1

End point title	Response rate - Clinical group 1
End point description: Clinical group (stratum) 1: (liver and/or lung metastasis potentially resectable after downsizing, comorbidity allowing surgery)	
End point type	Secondary
End point timeframe: from start of study treatment until end of follow-up	

End point values	FOLFOX+beva	FOLFOXIRI+beva		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: Subjects				
response	18	23		
failure	14	11		

Statistical analyses

Statistical analysis title	Response rate Stratum 1 - Fisher's exact
Comparison groups	FOLFOX+beva v FOLFOXIRI+beva
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.45
Method	Fisher exact

Secondary: Response rate - Clinical group 2

End point title	Response rate - Clinical group 2
End point description: Clinical group (stratum) 2: multiple metastasis, rapid progression, risk of rapid deterioration, unlikely to become resectable	
End point type	Secondary
End point timeframe: from start of study treatment until end of follow up	

End point values	FOLFOX+beva	FOLFOXIRI+beva		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	62		
Units: Subjects				
response	40	42		
failure	24	20		

Statistical analyses

Statistical analysis title	Response rate Stratum 2 - Fisher's exact
Comparison groups	FOLFOXIRI+beva v FOLFOX+beva
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.58
Method	Fisher exact

Secondary: Response rate - Clinical group 3

End point title	Response rate - Clinical group 3
End point description:	
Clinical group (stratum) 3: (not resectable and no symptoms or risk of deterioration)	
End point type	Secondary
End point timeframe:	
from start of study treatment until end of follow up	

End point values	FOLFOX+beva	FOLFOXIRI+beva		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: Subjects				
response	11	14		
failure	7	4		

Statistical analyses

Statistical analysis title	Response rate Stratum 3 - Fisher's exact
Comparison groups	FOLFOX+beva v FOLFOXIRI+beva

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.47
Method	Fisher exact

Secondary: Progression Free Survival - RAS wildtype

End point title	Progression Free Survival - RAS wildtype
End point description:	
End point type	Secondary
End point timeframe:	
from start of study treatment until end of follow-up	

End point values	FOLFOX+beva	FOLFOXIRI+beva		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	45		
Units: Subjects				
events	39	43		

Attachments (see zip file)	PFS - RAS wildtype/PFS-all-RAS-wt.JPG
-----------------------------------	---------------------------------------

Statistical analyses

Statistical analysis title	PFS - Hazard ratio, CI and p-value
Comparison groups	FOLFOX+beva v FOLFOXIRI+beva
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.18
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.15

Secondary: Progression Free Survival - RAS mutated

End point title	Progression Free Survival - RAS mutated
End point description:	
End point type	Secondary
End point timeframe:	
from start of study treatment until end of follow-up	

End point values	FOLFOX+beva	FOLFOXIRI+beva		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	61		
Units: Subjects				
events	52	55		

Attachments (see zip file)	PFS - RAS mutated/PFS-all-RAS-mut.JPG
-----------------------------------	---------------------------------------

Statistical analyses

Statistical analysis title	PFS - Hazard ratio, CI and p-value
Comparison groups	FOLFOX+beva v FOLFOXIRI+beva
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.53
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.3

Secondary: Progression Free Survival - BRAF mutated

End point title	Progression Free Survival - BRAF mutated
End point description:	
End point type	Secondary
End point timeframe:	
from start of study treatment until end of follow-up	

End point values	FOLFOX+beva	FOLFOXIRI+beva		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	8		
Units: Subjects				
events	4	7		

Attachments (see zip file)	PFS - BRAF mutated/PFS-BRAFmut.JPG
-----------------------------------	------------------------------------

Statistical analyses

Statistical analysis title	PFS - Hazard ratio, CI and p-value
Comparison groups	FOLFOX+beva v FOLFOXIRI+beva
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.61
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	2.54

Secondary: Progression free survival - Clinical group 1

End point title	Progression free survival - Clinical group 1
End point description:	Clinical group (stratum) 1: (liver and/or lung metastasis potentially resectable after downsizing, comorbidity allowing surgery)
End point type	Secondary
End point timeframe:	from start of study treatment until end of follow-up

End point values	FOLFOX+beva	FOLFOXIRI+beva		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: Subjects				
events	30	30		

Attachments (see zip file)	PFS - Stratum 1/PFS-Stratum 1.JPG
-----------------------------------	-----------------------------------

Statistical analyses

Statistical analysis title	PFS - Stratum 1 - Hazard ratio, CI and p-value
Comparison groups	FOLFOX+beva v FOLFOXIRI+beva
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.33

Secondary: Progression free survival - Clinical group 2

End point title	Progression free survival - Clinical group 2
End point description:	
Clinical group (stratum) 2: multiple metastasis, rapid progression, risk of rapid deterioration, unlikely to become resectable	
End point type	Secondary
End point timeframe:	
from start of study treatment until end of follow-up	

End point values	FOLFOX+beva	FOLFOXIRI+beva		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	67		
Units: Subjects				
events	60	64		

Attachments (see zip file)	PFS - Stratum 2/PFS-Stratum 2.JPG
-----------------------------------	-----------------------------------

Statistical analyses

Statistical analysis title	PFS - Stratum 2 - Hazard ratio, CI and p-value
Comparison groups	FOLFOXIRI+beva v FOLFOX+beva

Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.67
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.32

Secondary: Progression free survival - Clinical group 3

End point title	Progression free survival - Clinical group 3
End point description:	
Clinical group (stratum) 3: (not resectable and no symptoms or risk of deterioration	
End point type	Secondary
End point timeframe:	
from start of study treatment until end of follow up	

End point values	FOLFOX+beva	FOLFOXIRI+beva		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: Subjects				
events	18	18		

Attachments (see zip file)	PFS - Stratum 3/PFS-Stratum 3.JPG
-----------------------------------	-----------------------------------

Statistical analyses

Statistical analysis title	PFS - Stratum 3 - Hazard ratio, CI and p-value
Comparison groups	FOLFOX+beva v FOLFOXIRI+beva
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.097
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.55

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	1.12

Secondary: Overall Survival - RAS wildtype

End point title	Overall Survival - RAS wildtype
End point description:	
End point type	Secondary
End point timeframe:	
from start of study treatment until end of follow-up	

End point values	FOLFOX+beva	FOLFOXIRI+beva		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	45		
Units: Subjects				
events	37	35		

Attachments (see zip file)	OS - RAS wildtype/OS-all-RAS-wt.JPG
-----------------------------------	-------------------------------------

Statistical analyses

Statistical analysis title	OS - RAS wildtype - Hazard ratio, CI and p-value
Comparison groups	FOLFOX+beva v FOLFOXIRI+beva
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.29
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	1.24

Secondary: Overall Survival - RAS mutated

End point title	Overall Survival - RAS mutated
End point description:	
End point type	Secondary
End point timeframe:	
from start of study treatment until end of follow up	

End point values	FOLFOX+beva	FOLFOXIRI+beva		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	61		
Units: Subjects				
events	46	48		

Attachments (see zip file)	OS - RAS mutated/OS-all-RAS-mut.JPG
-----------------------------------	-------------------------------------

Statistical analyses

Statistical analysis title	OS - RAS mutated - Hazard ratio, CI and p-value
Comparison groups	FOLFOXIRI+beva v FOLFOX+beva
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.35
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.24

Secondary: Overall Survival - BRAF mutated

End point title	Overall Survival - BRAF mutated
End point description:	
End point type	Secondary
End point timeframe:	
from start of study treatment until end of follow-up	

End point values	FOLFOX+beva	FOLFOXIRI+beva		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	8		
Units: Subjects				
events	4	7		

Attachments (see zip file)	OS - BRAF mutated/OS-BRAFmut.JPG
-----------------------------------	----------------------------------

Statistical analyses

Statistical analysis title	OS - BRAF mutated - Hazard ratio, CI and p-value
Comparison groups	FOLFOX+beva v FOLFOXIRI+beva
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.99
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	3.48

Secondary: Overall survival - Clinical group 1

End point title	Overall survival - Clinical group 1
End point description:	
Clinical group (stratum) 1: (liver and/or lung metastasis potentially resectable after downsizing, comorbidity allowing surgery)	
End point type	Secondary
End point timeframe:	
from start of study treatment until end of follow up	

End point values	FOLFOX+beva	FOLFOXIRI+beva		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: Subjects				
events	27	22		

Attachments (see zip file)	OS - Stratum 1/OS-Stratum 1.JPG
-----------------------------------	---------------------------------

Statistical analyses

Statistical analysis title	OS - Stratum 1 - Hazard ratio, CI and p-value
Comparison groups	FOLFOXIRI+beva v FOLFOX+beva
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.19
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	1.21

Secondary: Overall survival - Clinical group 2

End point title	Overall survival - Clinical group 2
End point description:	
Clinical group (stratum) 2: multiple metastasis, rapid progression, risk of rapid deterioration, unlikely to become resectable	
End point type	Secondary
End point timeframe:	
from start of study treatment until end of follow up	

End point values	FOLFOX+beva	FOLFOXIRI+beva		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	67		
Units: Subjects				
events	54	59		

Attachments (see zip file)	OS - Stratum 2/OS-Stratum 2.JPG
-----------------------------------	---------------------------------

Statistical analyses

Statistical analysis title	OS - Stratum 2 - Hazard ratio, CI and p-value
Comparison groups	FOLFOX+beva v FOLFOXIRI+beva

Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.56
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.3

Secondary: Overall survival - Clinical group 3

End point title	Overall survival - Clinical group 3
End point description:	
Clinical group (stratum) 3: (not resectable and no symptoms or risk of deterioration	
End point type	Secondary
End point timeframe:	
from start of study treatment until end of follow up	

End point values	FOLFOX+beva	FOLFOXIRI+beva		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: Subjects				
events	17	15		

Attachments (see zip file)	OS - Stratum 3/OS-Stratum 3.JPG
-----------------------------------	---------------------------------

Statistical analyses

Statistical analysis title	OS - Stratum 3 - Hazard ratio, CI and p-value
Comparison groups	FOLFOX+beva v FOLFOXIRI+beva
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.33
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	1.43

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Start date occurred during treatment plus 30 days, or between end of induction and start of maintenance. Any events after start of maintenance were counted for this part of therapy, also with a wash-out-period of 30 days.

Adverse event reporting additional description:

All subjects received at least one dose of study treatment were analysed for safety. One subject received irinotecan in the first cycle although being randomised to arm A; subject was included in safety analysis as being randomised to arm B according to protocol.

Assessment type	Non-systematic
-----------------	----------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	14.1
--------------------	------

Reporting groups

Reporting group title	FOLFOX+beva
-----------------------	-------------

Reporting group description:

Induction chemotherapy: FOLFOX (oxaliplatin, LV and 5-FU and bevacizumab, biweekly), until progression, intolerable toxicity, and secondary resection or for a max. of 12 cycles (6 months). Maintenance therapy: either 5-FU/LV and bevacizumab (biweekly) or capecitabine and bevacizumab (5-FU or capecitabine at the investigators discretion) for up to 12 months until progression or intolerable toxicity. Maximum treatment duration: 18 months (6 months of FOLFOX and bevacizumab and 12 months of maintenance). In case of secondary resection treatment had to be resumed 4–8 weeks postoperatively for a total of 6 months FOLFOX and bevacizumab (pre- and post-op treatment), followed by maintenance treatment for total treatment duration of up to 12 months in the absence of progression or intolerable toxicity.

Reporting group title	FOLFOXIRI+beva
-----------------------	----------------

Reporting group description:

Induction chemotherapy: FOLFOX (oxaliplatin, LV and 5-FU and bevacizumab + irinotecan, biweekly), until progression, intolerable toxicity, and secondary resection or for a max. of 12 cycles (6 months). Maintenance therapy: either 5-FU/LV and bevacizumab (biweekly) or capecitabine and bevacizumab (5-FU or capecitabine at the investigators discretion) for up to 12 months until progression or intolerable toxicity. Maximum treatment duration: 18 months (6 months of FOLFOX and bevacizumab + irinotecan + 12 M of maintenance). In case of secondary resection treatment had to be resumed 4–8 weeks postoperatively for a total of 6 months FOLFOX and bevacizumab + irinotecan (pre- and post-op treatment), followed by maintenance treatment for total treatment duration of up to 12 months in the absence of progression or intolerable toxicity.

Serious adverse events	FOLFOX+beva	FOLFOXIRI+beva	
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 119 (23.53%)	37 / 123 (30.08%)	
number of deaths (all causes)	98	96	
number of deaths resulting from adverse events	2	4	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	1 / 119 (0.84%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Tumour progression subjects affected / exposed	3 / 119 (2.52%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 119 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 119 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	1 / 119 (0.84%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever of unknown origin			
subjects affected / exposed	1 / 119 (0.84%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis in device			
subjects affected / exposed	1 / 119 (0.84%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 119 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 119 (0.84%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Drug intolerance			
subjects affected / exposed	1 / 119 (0.84%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reduced general condition			
subjects affected / exposed	2 / 119 (1.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 119 (0.84%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	1 / 119 (0.84%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 119 (0.84%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death unexplained			
subjects affected / exposed	0 / 119 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	2 / 119 (1.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatic hypoplasia			
subjects affected / exposed	0 / 119 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	2 / 119 (1.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 119 (0.84%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mental disorder			
subjects affected / exposed	0 / 119 (0.00%)	1 / 123 (0.81%)	
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			
Radiation pneumonitis			
subjects affected / exposed	0 / 119 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax traumatic			
subjects affected / exposed	1 / 119 (0.84%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 119 (0.84%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical vertebral fracture			
subjects affected / exposed	1 / 119 (0.84%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anastomotic complication			

subjects affected / exposed	1 / 119 (0.84%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	1 / 119 (0.84%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Ventricular fibrillation			
subjects affected / exposed	0 / 119 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 119 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 119 (0.00%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 119 (0.84%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Organic brain syndrome			
subjects affected / exposed	1 / 119 (0.84%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	0 / 119 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Neuroleptic malignant syndrome			
subjects affected / exposed	0 / 119 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 119 (1.68%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cerebral infarction			
subjects affected / exposed	0 / 119 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 119 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 119 (0.84%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 119 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 119 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 119 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			

subjects affected / exposed	0 / 119 (0.00%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic fever			
subjects affected / exposed	1 / 119 (0.84%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 119 (4.20%)	9 / 123 (7.32%)	
occurrences causally related to treatment / all	5 / 5	11 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon perforation			
subjects affected / exposed	1 / 119 (0.84%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	3 / 119 (2.52%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emesis			
subjects affected / exposed	2 / 119 (1.68%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vomiting			
subjects affected / exposed	2 / 119 (1.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 119 (0.84%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	0 / 119 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 119 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical ileus			
subjects affected / exposed	0 / 119 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 119 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nausea			
subjects affected / exposed	2 / 119 (1.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal toxicity			
subjects affected / exposed	0 / 119 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal pain			
subjects affected / exposed	0 / 119 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fistula of small intestine			
subjects affected / exposed	1 / 119 (0.84%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			

subjects affected / exposed	1 / 119 (0.84%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 119 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 119 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 119 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 119 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Biloma			
subjects affected / exposed	0 / 119 (0.00%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal disorder			
subjects affected / exposed	1 / 119 (0.84%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 119 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			

subjects affected / exposed	2 / 119 (1.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 119 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 119 (0.84%)	0 / 123 (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			
Anal abscess			
subjects affected / exposed	1 / 119 (0.84%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	5 / 119 (4.20%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	3 / 5	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 119 (0.84%)	4 / 123 (3.25%)	
occurrences causally related to treatment / all	2 / 2	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	0 / 119 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Febrile infection			
subjects affected / exposed	0 / 119 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Postoperative wound infection			
subjects affected / exposed	0 / 119 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 119 (2.52%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal infection			
subjects affected / exposed	0 / 119 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral herpes			
subjects affected / exposed	1 / 119 (0.84%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary infection			
subjects affected / exposed	1 / 119 (0.84%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 119 (0.84%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	0 / 119 (0.00%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 119 (0.84%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			

subjects affected / exposed	0 / 119 (0.00%)	1 / 123 (0.81%)	
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 / 119 (0.84%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 119 (0.84%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	1 / 119 (0.84%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma infection			
subjects affected / exposed	0 / 119 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis Escherichia coli			
subjects affected / exposed	0 / 119 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 119 (0.84%)	0 / 123 (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			
Hyperglycaemia			
subjects affected / exposed	1 / 119 (0.84%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic complication			

subjects affected / exposed	1 / 119 (0.84%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 119 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 119 (0.00%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	FOLFOX+beva	FOLFOXIRI+beva	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	119 / 119 (100.00%)	123 / 123 (100.00%)	
Investigations			
C-reactive protein increased			
subjects affected / exposed	6 / 119 (5.04%)	2 / 123 (1.63%)	
occurrences (all)	6	2	
Weight decreased			
subjects affected / exposed	8 / 119 (6.72%)	6 / 123 (4.88%)	
occurrences (all)	8	6	
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 119 (5.88%)	17 / 123 (13.82%)	
occurrences (all)	7	17	
Nervous system disorders			
Dizziness			
subjects affected / exposed	11 / 119 (9.24%)	9 / 123 (7.32%)	
occurrences (all)	11	9	
Dysgeusia			
subjects affected / exposed	13 / 119 (10.92%)	13 / 123 (10.57%)	
occurrences (all)	13	13	

Headache			
subjects affected / exposed	13 / 119 (10.92%)	5 / 123 (4.07%)	
occurrences (all)	13	5	
Neuropathy peripheral			
subjects affected / exposed	10 / 119 (8.40%)	7 / 123 (5.69%)	
occurrences (all)	10	7	
Paraesthesia			
subjects affected / exposed	12 / 119 (10.08%)	14 / 123 (11.38%)	
occurrences (all)	12	14	
Peripheral sensory neuropathy			
subjects affected / exposed	7 / 119 (5.88%)	2 / 123 (1.63%)	
occurrences (all)	7	2	
Polyneuropathy			
subjects affected / exposed	47 / 119 (39.50%)	39 / 123 (31.71%)	
occurrences (all)	47	39	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 119 (7.56%)	16 / 123 (13.01%)	
occurrences (all)	9	16	
Leukopenia			
subjects affected / exposed	9 / 119 (7.56%)	24 / 123 (19.51%)	
occurrences (all)	9	24	
Neutropenia			
subjects affected / exposed	17 / 119 (14.29%)	38 / 123 (30.89%)	
occurrences (all)	17	38	
Thrombocytopenia			
subjects affected / exposed	16 / 119 (13.45%)	17 / 123 (13.82%)	
occurrences (all)	16	17	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	7 / 119 (5.88%)	12 / 123 (9.76%)	
occurrences (all)	7	12	
Fatigue			
subjects affected / exposed	31 / 119 (26.05%)	26 / 123 (21.14%)	
occurrences (all)	31	26	
General physical health deterioration			

subjects affected / exposed occurrences (all)	7 / 119 (5.88%) 7	5 / 123 (4.07%) 5	
Mucosal inflammation subjects affected / exposed occurrences (all)	18 / 119 (15.13%) 18	18 / 123 (14.63%) 18	
Pain subjects affected / exposed occurrences (all)	8 / 119 (6.72%) 8	5 / 123 (4.07%) 5	
Pyrexia subjects affected / exposed occurrences (all)	14 / 119 (11.76%) 14	12 / 123 (9.76%) 12	
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	12 / 119 (10.08%) 12	13 / 123 (10.57%) 13	
Abdominal pain upper subjects affected / exposed occurrences (all)	3 / 119 (2.52%) 3	10 / 123 (8.13%) 10	
Diarrhoea subjects affected / exposed occurrences (all)	43 / 119 (36.13%) 43	71 / 123 (57.72%) 71	
Nausea subjects affected / exposed occurrences (all)	54 / 119 (45.38%) 54	55 / 123 (44.72%) 55	
Stomatitis subjects affected / exposed occurrences (all)	11 / 119 (9.24%) 11	14 / 123 (11.38%) 14	
Vomiting subjects affected / exposed occurrences (all)	26 / 119 (21.85%) 26	30 / 123 (24.39%) 30	
Respiratory, thoracic and mediastinal disorders			
Constipation subjects affected / exposed occurrences (all)	19 / 119 (15.97%) 19	9 / 123 (7.32%) 9	
Epistaxis			

subjects affected / exposed	22 / 119 (18.49%)	9 / 123 (7.32%)	
occurrences (all)	22	9	
Oropharyngeal pain			
subjects affected / exposed	7 / 119 (5.88%)	1 / 123 (0.81%)	
occurrences (all)	7	1	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	12 / 119 (10.08%)	27 / 123 (21.95%)	
occurrences (all)	12	27	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	8 / 119 (6.72%)	4 / 123 (3.25%)	
occurrences (all)	8	4	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 119 (5.88%)	1 / 123 (0.81%)	
occurrences (all)	7	1	
Infections and infestations			
Infection			
subjects affected / exposed	9 / 119 (7.56%)	5 / 123 (4.07%)	
occurrences (all)	9	5	
Nasopharyngitis			
subjects affected / exposed	14 / 119 (11.76%)	7 / 123 (5.69%)	
occurrences (all)	14	7	
Urinary tract infection			
subjects affected / exposed	7 / 119 (5.88%)	5 / 123 (4.07%)	
occurrences (all)	7	5	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	15 / 119 (12.61%)	16 / 123 (13.01%)	
occurrences (all)	15	16	
Hyperkalaemia			
subjects affected / exposed	7 / 119 (5.88%)	13 / 123 (10.57%)	
occurrences (all)	7	13	

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

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/22897915>