Clinical trial results:
Sequential first-line therapy in metastatic colorectal cancer with Capecitabine/FUFA, Irinotecan and Bevacizumab
- Capecitabine/FUFA plus Bevacizumab versus Capecitabine/FUFA plus Irinotecan plus Bevacizumab as first-line therapy in metastatic colorectal cancer -

Summary

EudraCT number	2009-013099-38
Trial protocol	DE
Global end of trial date	16 September 2020

Results information

Result version number	v1 (current)
This version publication date	29 September 2021
First version publication date	29 September 2021
Summary attachment (see zip file)	Final Report ACCORDING TO § 42B (2) German Drug Law (AB_ML22011_2021_07_01.pdf)

Trial information

Trial identification

Sponsor protocol code	ML22011

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Klinikum der Universität München - Grosshadern
Sponsor organisation address	Marchioninistraße 15, München, Germany, 81377
Public contact	Medizinische Klinik III AG Onkologie, Klinikum der Universität München - Grosshadern, +49 89 4400 0, onkologiestudien@med.uni-muenchen.de
Scientific contact	Medizinische Klinik III AG Onkologie, Klinikum der Universität München - Grosshadern, +49 89 4400 0, onkologiestudien@med.uni-muenchen.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	27 January 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 September 2020
Global end of trial reached?	Yes
Global end of trial date	16 September 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluation of effectiveness in correlation to tolerability of both therapy schemes in patients with metastatic colorectal cancer without Prior therapy.

Protection of trial subjects:

The present study was developed for those patients, who do not necessarily require treatment with primary combination chemotherapy according to the recommendations of the S3 guideline (Group 3, Schmiegel 2008). Patients with multiple metastases that are not primarily resectable and for whom the option for resection after the metastases have regressed is unlikely. The patients should be in a good general state of health (ECOG 0-1) and exhibit an oligo- or asymptomatic disease (group 3 according to the S3 guideline).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 December 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	36 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 434
Worldwide total number of subjects	434
EEA total number of subjects	434

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)	293
From 65 to 84 years	138
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Investigating an optimal first-line treatment, the current study compares a sequential escalation strategy starting with FP 1 Bev plus the addition of Iri at disease progression with initial use of the three-drug regimen (FP 1 Iri 1 Bev).

Pre-assignment period milestones

Number of subjects started	434
Number of subjects completed	421

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Protocol deviation: 1
Reason: Number of subjects	Terminated study before treatment start: 12

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Capecitabine plus bevacizumab

Arm description:

Capecitabine: 2 x 1,250 mg/m2Day 1-14 followed by a 1 week break
Bevacizumab: 7.5 mg/kg Day 1
The regimen is repeated at 3-week intervals

Treatment will be continued until progression or toxicity. If progression occurs, the scheme will be escalated: from capecitabine plus bevacizumab to XELIRI plus bevacizumab or from FUFA plus bevacizumab to FOLFIRI and bevacizumab.

Arm type	Experimental
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Capecitabine: 2 x 1,250 mg/m2Day 1-14 followed by a 1 week break

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

Bevacizumab: 7.5 mg/kg Day 1

Arm title	5-FUFA plus bevacizumab

Arm description:

Folinic acid (racemic) 400 mg/m² IV, 120 min Day 1
5-FU 400 mg/m² bolus Day 1
5-FU 2,400 mg/m² IV for 46 h Day 1-2
Bevacizumab: 5.0 mg/kg Day 1
The regimen is repeated at 2-week intervals

Treatment will be continued until progression or toxicity. If progression occurs, the scheme will be escalated: from capecitabine plus bevacizumab to XELIRI plus bevacizumab or from FUFA plus bevacizumab to FOLFIRI and bevacizumab

Arm type	Active comparator
Investigational medicinal product name	5-FU bolus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details:

5-FU 400 mg/m² bolus Day 1

Investigational medicinal product name	5-FU
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

5-FU 2,400 mg/m² IV for 46 h Day 1-2

Investigational medicinal product name	Folinic acid (racemic)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

Folinic acid (racemic) 400 mg/m² IV, 120 min Day 1

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

Bevacizumab: 5.0 mg/kg Day 1

Number of subjects in period 1[1]	Capecitabine plus bevacizumab	5-FUFA plus bevacizumab
Started	212	209
Completed	212	209

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Transmitted numbers of subjects are correct.

Baseline characteristics

Reporting groups

Reporting group title	Capecitabine plus bevacizumab

Reporting group description:

Capecitabine: 2 x 1,250 mg/m2 Day 1-14 followed by a 1 week break
Bevacizumab: 7.5 mg/kg Day 1
The regimen is repeated at 3-week intervals

Treatment will be continued until progression or toxicity. If progression occurs, the scheme will be escalated: from capecitabine plus bevacizumab to XELIRI plus bevacizumab or from FUFA plus bevacizumab to FOLFIRI and bevacizumab.

Reporting group title	5-FUFA plus bevacizumab

Reporting group description:

Folinic acid (racemic) 400 mg/m² IV, 120 min Day 1
5-FU 400 mg/m² bolus Day 1
5-FU 2,400 mg/m² IV for 46 h Day 1-2
Bevacizumab: 5.0 mg/kg Day 1
The regimen is repeated at 2-week intervals

Treatment will be continued until progression or toxicity. If progression occurs, the scheme will be escalated: from capecitabine plus bevacizumab to XELIRI plus bevacizumab or from FUFA plus bevacizumab to FOLFIRI and bevacizumab

Reporting group values	Capecitabine plus bevacizumab	5-FUFA plus bevacizumab	Total
Number of subjects	212	209	421
Age categorical Units: Subjects			
Adults (18-64 years)	151	132	283
From 65-84 years	60	75	135
85 years and over	1	2	3
Age continuous Units: years			
median	71	69	
full range (min-max)	43 to 87	42 to 88	-
Gender categorical Units: Subjects			
Female	137	144	281
Male	75	65	140
ECOG Performance status Units: Subjects			
ECOG 0	127	124	251
ECOG 1	85	83	168
unkown	0	2	2
Onset of metastases Units: Subjects			
Synchronous	151	145	296
Metachronous	57	59	116
Unknown	4	5	9
Site of primary tumor Units: Subjects			
Left (splenic flexurerectum)	140	138	278

Right (transverse coloncecum)	68	64	132
Unknown	4	7	11
No. of metastatic sites Units: Subjects			
1 Metastase	74	75	149
>= 2 Metastases	133	126	259
unkown	5	8	13
Fluoropyrimidine used Units: Subjects			
Capecitabine	151	136	287
Infusional fluorouracil	61	73	134

End points

End points reporting groups

Reporting group title	Capecitabine plus bevacizumab

Reporting group description:

Capecitabine: 2 x 1,250 mg/m2 Day 1-14 followed by a 1 week break
Bevacizumab: 7.5 mg/kg Day 1
The regimen is repeated at 3-week intervals

Treatment will be continued until progression or toxicity. If progression occurs, the scheme will be escalated: from capecitabine plus bevacizumab to XELIRI plus bevacizumab or from FUFA plus bevacizumab to FOLFIRI and bevacizumab.

Reporting group title	5-FUFA plus bevacizumab

Reporting group description:

Folinic acid (racemic) 400 mg/m² IV, 120 min	Day 1
5-FU 400 mg/m² bolus	Day 1
5-FU 2,400 mg/m² IV for 46 h	Day 1-2
Bevacizumab: 5.0 mg/kg	Day 1

The regimen is repeated at 2-week intervals

Treatment will be continued until progression or toxicity. If progression occurs, the scheme will be escalated: from capecitabine plus bevacizumab to XELIRI plus bevacizumab or from FUFA plus bevacizumab to FOLFIRI and bevacizumab

Primary: Time to failure of strategy

End point title	Time to failure of strategy

End point description:

- Time to failure of treatment strategy (TFS) will be determined as the primary endpoint. In the control arm, this corresponds to the time from randomisation to definitive progression under XELIRI/FOLFIRI + bevacizumab (PFS-1) (allowing for the possible resumption after initial response, pause of therapy and subsequent progression). In the experimental arm, an escalation to the combination XELIRI or FOLFIRI + bevacizumab can take place, if capecitabine/FUFA + bevacizumab fails (PFS-1). Failure of this treatment strategy is defined as second progression (PFS-2).
- If a comparable TFS is achieved in both treatment arms, a side effect analysis will be used to help in defining the better treatment strategy. Treatment-associated toxicity will be evaluated as analysis of all grade 2-5 toxicities (according to NCI CTCAE, Version 4.0) divided by the number of treatment cycles administered during the total TFS period.

End point type	Primary

End point timeframe:

the time from randomisation to definitive progression under XELIRI/FOLFIRI + bevacizumab (PFS-1) . In the experimental arm, an escalation to the combination XELIRI or FOLFIRI + bevacizumab can take place, if capecitabine/FUFA + bevacizumab fails (PFS-1)

End point values	Capecitabine plus bevacizumab	5-FUFA plus bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	186		
Units: months				
median (confidence interval 90%)	9.6 (8.6 to 10.6)	9.9 (8.8 to 10.6)		

Attachments (see zip file)	Kaplan-Meier-TFS/TFS ML22011.png

Statistical analyses

Statistical analysis title	TFS
Comparison groups	Capecitabine plus bevacizumab v 5-FUFA plus bevacizumab
Number of subjects included in analysis	380
Analysis specification	Post-hoc
Analysis type	equivalence
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.73
upper limit	1.02
Variability estimate	Standard deviation

Secondary: Response Data

End point title	Response Data

End point description:

End point type	Secondary

End point timeframe:

- Overall survival (OS) in both treatment arms, including 60-day mortality
- PFS-1 (progression-free survival) in both treatment arms (decentralised recording by study sites)

End point values	Capecitabine plus bevacizumab	5-FUFA plus bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	209		
Units: months				
median (confidence interval 95%)				
OS	21.9 (20.2 to 25.0)	23.5 (20.9 to 27.9)		
PFS-1	8.0 (6.9 to 9.9)	9.9 (8.7 to 10.9)		

Statistical analyses

Statistical analysis title	Overall Response Rate - ORR
Comparison groups	Capecitabine plus bevacizumab v 5-FUFA plus bevacizumab
Number of subjects included in analysis	421
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.005
Method	Logrank
Parameter estimate	Odds ratio (OR)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	0.74
Variability estimate	Standard deviation

Statistical analysis title	Progression Free Survival - PFS1
Comparison groups	Capecitabine plus bevacizumab v 5-FUFA plus bevacizumab
Number of subjects included in analysis	421
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	< 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	0.85
Variability estimate	Standard deviation

Statistical analysis title	Overall Survival - OS
Comparison groups	Capecitabine plus bevacizumab v 5-FUFA plus bevacizumab

Number of subjects included in analysis	421
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.14
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.06
Variability estimate	Standard deviation

Secondary: objective response rate (ORR)

End point title	objective response rate (ORR)

End point description:

End point type	Secondary

End point timeframe:

- Response rate (ORR) (decentralised recording by study sites)

End point values	Capecitabine plus bevacizumab	5-FUFA plus bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	209		
Units: subjects				
CR/PR	80	117		

Statistical analyses

Statistical analysis title	Objective Response Rate - ORR
Comparison groups	5-FUFA plus bevacizumab v Capecitabine plus bevacizumab
Number of subjects included in analysis	421
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.0002
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	0.477

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.323
upper limit	0.704
Variability estimate	Standard deviation

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events include all events that occur in a patient / participant in a clinical study following administration of a medicinal product. A causal association with this treatment is not a requirement here.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	Capecitabine plus bevacizumab

Reporting group description:

Capecitabine: 2 x 1,250 mg/m2 Day 1-14 followed by a 1 week break
Bevacizumab: 7.5 mg/kg Day 1
The regimen is repeated at 3-week intervals

Treatment will be continued until progression or toxicity. If progression occurs, the scheme will be escalated: from capecitabine plus bevacizumab to XELIRI plus bevacizumab or from FUFA plus bevacizumab to FOLFIRI and bevacizumab.

Reporting group title	5-FUFA plus bevacizumab

Reporting group description:

Folinic acid (racemic) 400 mg/m² IV, 120 min Day 1
5-FU 400 mg/m² bolus Day 1
5-FU 2,400 mg/m² IV for 46 h Day 1-2
Bevacizumab: 5.0 mg/kg Day 1
The regimen is repeated at 2-week intervals

Treatment will be continued until progression or toxicity. If progression occurs, the scheme will be escalated: from capecitabine plus bevacizumab to XELIRI plus bevacizumab or from FUFA plus bevacizumab to FOLFIRI and bevacizumab

Serious adverse events	Capecitabine plus bevacizumab	5-FUFA plus bevacizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 212 (13.68%)	68 / 210 (32.38%)	
number of deaths (all causes)	3	4	
number of deaths resulting from adverse events	1	3	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	8 / 212 (3.77%)	4 / 210 (1.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiccups			

subjects affected / exposed	2 / 212 (0.94%)	4 / 210 (1.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myopathy			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	3 / 212 (1.42%)	6 / 210 (2.86%)	
occurrences causally related to treatment / all	0 / 81	2 / 103	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 212 (0.47%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
other			
subjects affected / exposed	6 / 212 (2.83%)	3 / 210 (1.43%)	
occurrences causally related to treatment / all	0 / 37	0 / 25	
deaths causally related to treatment / all	0 / 2	0 / 0	
Respiratory distress			
subjects affected / exposed	2 / 212 (0.94%)	5 / 210 (2.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 212 (0.47%)	2 / 210 (0.95%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vomiting			
subjects affected / exposed	4 / 212 (1.89%)	5 / 210 (2.38%)	
occurrences causally related to treatment / all	1 / 35	2 / 53	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound healing complications			

subjects affected / exposed	5 / 212 (2.36%)	5 / 210 (2.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Chills			
subjects affected / exposed	5 / 212 (2.36%)	6 / 210 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	4 / 212 (1.89%)	5 / 210 (2.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	20 / 212 (9.43%)	19 / 210 (9.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever			
subjects affected / exposed	24 / 212 (11.32%)	38 / 210 (18.10%)	
occurrences causally related to treatment / all	0 / 3	4 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	10 / 212 (4.72%)	17 / 210 (8.10%)	
occurrences causally related to treatment / all	1 / 6	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hand-Foot-Syndrome			
subjects affected / exposed	26 / 212 (12.26%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 100	0 / 61	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucositis/Stomatitis			
subjects affected / exposed	1 / 212 (0.47%)	2 / 210 (0.95%)	
occurrences causally related to treatment / all	0 / 64	1 / 50	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			

Sudden death			
subjects affected / exposed	2 / 212 (0.94%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Fall			
subjects affected / exposed	5 / 212 (2.36%)	3 / 210 (1.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Withdrawal syndrome			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Enterocele			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device implantation			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural site reaction			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
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			
Femoral neck fracture			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	7 / 212 (3.30%)	2 / 210 (0.95%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure increased			
subjects affected / exposed	4 / 212 (1.89%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorder			
subjects affected / exposed	2 / 212 (0.94%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 212 (0.47%)	2 / 210 (0.95%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac toxicity			
subjects affected / exposed	13 / 212 (6.13%)	11 / 210 (5.24%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardial-ischemic event			
subjects affected / exposed	3 / 212 (1.42%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Cardiovascular disorder			
subjects affected / exposed	2 / 212 (0.94%)	4 / 210 (1.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	4 / 212 (1.89%)	2 / 210 (0.95%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 212 (0.94%)	3 / 210 (1.43%)	
occurrences causally related to treatment / all	0 / 137	1 / 135	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 212 (0.94%)	7 / 210 (3.33%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 32	0 / 26	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	3 / 212 (1.42%)	3 / 210 (1.43%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental disorder			
subjects affected / exposed	2 / 212 (0.94%)	3 / 210 (1.43%)	
occurrences causally related to treatment / all	0 / 128	0 / 123	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			

subjects affected / exposed	27 / 212 (12.74%)	18 / 210 (8.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological disorder			
subjects affected / exposed	5 / 212 (2.36%)	3 / 210 (1.43%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	10 / 212 (4.72%)	9 / 210 (4.29%)	
occurrences causally related to treatment / all	0 / 125	0 / 121	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	4 / 212 (1.89%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Abscesses fistulae			
subjects affected / exposed	7 / 212 (3.30%)	7 / 210 (3.33%)	
occurrences causally related to treatment / all	1 / 5	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal haemorrhage			
subjects affected / exposed	2 / 212 (0.94%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ascites			
subjects affected / exposed	3 / 212 (1.42%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bleeding/hemorrhage			
subjects affected / exposed	6 / 212 (2.83%)	3 / 210 (1.43%)	
occurrences causally related to treatment / all	0 / 44	1 / 45	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bicarbonate decreased			

subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	1 / 212 (0.47%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 31	0 / 27	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	2 / 212 (0.94%)	11 / 210 (5.24%)	
occurrences causally related to treatment / all	0 / 0	3 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematologic toxicity			
subjects affected / exposed	5 / 212 (2.36%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 147	0 / 161	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatologic toxicity			
subjects affected / exposed	2 / 212 (0.94%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 128	0 / 123	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	5 / 212 (2.36%)	4 / 210 (1.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	26 / 212 (12.26%)	23 / 210 (10.95%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PCO2 decreased			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PO2 decreased			

subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	2 / 212 (0.94%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thromboembolic event			
subjects affected / exposed	18 / 212 (8.49%)	21 / 210 (10.00%)	
occurrences causally related to treatment / all	5 / 37	4 / 33	
deaths causally related to treatment / all	0 / 1	0 / 1	
Thrombosis (any)			
subjects affected / exposed	5 / 212 (2.36%)	5 / 210 (2.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 212 (0.47%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Cholangitis			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	1 / 212 (0.47%)	2 / 210 (0.95%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			

subjects affected / exposed	28 / 212 (13.21%)	46 / 210 (21.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	21 / 212 (9.91%)	17 / 210 (8.10%)	
occurrences causally related to treatment / all	1 / 111	5 / 124	
deaths causally related to treatment / all	0 / 2	0 / 0	
GI perforation			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	2 / 212 (0.94%)	2 / 210 (0.95%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	10 / 212 (4.72%)	8 / 210 (3.81%)	
occurrences causally related to treatment / all	1 / 10	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 1	
Intestinal ischaemia			
subjects affected / exposed	2 / 212 (0.94%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 212 (0.47%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin reaction			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 58	1 / 59	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Calculus ureteric			
subjects affected / exposed	2 / 212 (0.94%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	1 / 212 (0.47%)	4 / 210 (1.90%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal disorder			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	2 / 212 (0.94%)	5 / 210 (2.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Urinary retention			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract disorder			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (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			
Febrile infection			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fistula			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			

subjects affected / exposed	14 / 212 (6.60%)	16 / 210 (7.62%)	
occurrences causally related to treatment / all	1 / 102	1 / 102	
deaths causally related to treatment / all	0 / 1	0 / 1	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Capecitabine plus bevacizumab	5-FUFA plus bevacizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	212 / 212 (100.00%)	210 / 210 (100.00%)	
Surgical and medical procedures			
Anastomotic complication			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences (all)	0	1	
Catheter site ulcer			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Ageusia			
subjects affected / exposed	2 / 212 (0.94%)	4 / 210 (1.90%)	
occurrences (all)	2	4	
Allergy			
subjects affected / exposed	1 / 212 (0.47%)	2 / 210 (0.95%)	
occurrences (all)	1	2	
Alopecia			
subjects affected / exposed	52 / 212 (24.53%)	89 / 210 (42.38%)	
occurrences (all)	52	89	
Anxiety			
subjects affected / exposed	2 / 212 (0.94%)	3 / 210 (1.43%)	
occurrences (all)	2	3	
Bronchospasm			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences (all)	0	1	
Cachexia			
subjects affected / exposed	1 / 212 (0.47%)	1 / 210 (0.48%)	
occurrences (all)	1	1	

Chest discomfort			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences (all)	0	0	
Death/Sudden death			
subjects affected / exposed	2 / 212 (0.94%)	0 / 210 (0.00%)	
occurrences (all)	2	0	
Decreased appetite			
subjects affected / exposed	34 / 212 (16.04%)	43 / 210 (20.48%)	
occurrences (all)	34	43	
Dehydration			
subjects affected / exposed	2 / 212 (0.94%)	11 / 210 (5.24%)	
occurrences (all)	2	11	
Dizziness			
subjects affected / exposed	32 / 212 (15.09%)	26 / 210 (12.38%)	
occurrences (all)	32	26	
Dry mouth			
subjects affected / exposed	5 / 212 (2.36%)	7 / 210 (3.33%)	
occurrences (all)	5	7	
Dysgeusia			
subjects affected / exposed	20 / 212 (9.43%)	13 / 210 (6.19%)	
occurrences (all)	20	13	
Dyspepsia			
subjects affected / exposed	9 / 212 (4.25%)	9 / 210 (4.29%)	
occurrences (all)	9	9	
Dysphagia			
subjects affected / exposed	4 / 212 (1.89%)	5 / 210 (2.38%)	
occurrences (all)	4	5	
Dysphonia			
subjects affected / exposed	18 / 212 (8.49%)	8 / 210 (3.81%)	
occurrences (all)	18	8	
Dyspnoea			
subjects affected / exposed	20 / 212 (9.43%)	19 / 210 (9.05%)	
occurrences (all)	20	19	
Dyspnoea exertional			
subjects affected / exposed	5 / 212 (2.36%)	5 / 210 (2.38%)	
occurrences (all)	5	5	

Dysuria			
subjects affected / exposed	1 / 212 (0.47%)	4 / 210 (1.90%)	
occurrences (all)	1	4	
Eating disorder			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences (all)	0	1	
Enterocele			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences (all)	0	1	
Eructation			
subjects affected / exposed	1 / 212 (0.47%)	1 / 210 (0.48%)	
occurrences (all)	1	1	
Extravasation			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Faecal incontinence			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Faecaloma			
subjects affected / exposed	1 / 212 (0.47%)	4 / 210 (1.90%)	
occurrences (all)	1	4	
Faeces discoloured			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	8 / 212 (3.77%)	4 / 210 (1.90%)	
occurrences (all)	8	4	
Feeling cold			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences (all)	0	1	
Fistula			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences (all)	0	1	
Flatulence			
subjects affected / exposed	2 / 212 (0.94%)	2 / 210 (0.95%)	
occurrences (all)	2	2	

Flushing			
subjects affected / exposed	1 / 212 (0.47%)	3 / 210 (1.43%)	
occurrences (all)	1	3	
Frequent bowel movements			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences (all)	0	1	
Gait disturbance			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences (all)	0	1	
General physical health deterioration			
subjects affected / exposed	1 / 212 (0.47%)	17 / 210 (8.10%)	
occurrences (all)	1	17	
Haemorrhoids			
subjects affected / exposed	4 / 212 (1.89%)	3 / 210 (1.43%)	
occurrences (all)	4	3	
Hallucination			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Hand-foot syndrome			
subjects affected / exposed	100 / 212 (47.17%)	61 / 210 (29.05%)	
occurrences (all)	100	61	
Hernia			
subjects affected / exposed	2 / 212 (0.94%)	0 / 210 (0.00%)	
occurrences (all)	2	0	
Hiccups			
subjects affected / exposed	2 / 212 (0.94%)	4 / 210 (1.90%)	
occurrences (all)	2	4	
Hot flush			
subjects affected / exposed	1 / 212 (0.47%)	1 / 210 (0.48%)	
occurrences (all)	1	1	
Hyperaesthesia			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences (all)	0	1	
Hypercalcaemia			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	

Hyperglycaemia			
subjects affected / exposed	1 / 212 (0.47%)	2 / 210 (0.95%)	
occurrences (all)	1	2	
Hyperhidrosis			
subjects affected / exposed	1 / 212 (0.47%)	6 / 210 (2.86%)	
occurrences (all)	1	6	
Hyperkalaemia			
subjects affected / exposed	3 / 212 (1.42%)	4 / 210 (1.90%)	
occurrences (all)	3	4	
Hypertension			
subjects affected / exposed	137 / 212 (64.62%)	135 / 210 (64.29%)	
occurrences (all)	137	135	
Hyperuricemia			
subjects affected / exposed	24 / 212 (11.32%)	25 / 210 (11.90%)	
occurrences (all)	24	25	
Hypoaesthesia			
subjects affected / exposed	7 / 212 (3.30%)	9 / 210 (4.29%)	
occurrences (all)	7	9	
Hypoalbuminaemia			
subjects affected / exposed	2 / 212 (0.94%)	6 / 210 (2.86%)	
occurrences (all)	2	6	
Hypocalcaemia			
subjects affected / exposed	7 / 212 (3.30%)	9 / 210 (4.29%)	
occurrences (all)	7	9	
Hypomagnesaemia			
subjects affected / exposed	3 / 212 (1.42%)	1 / 210 (0.48%)	
occurrences (all)	3	1	
Hyponatraemia			
subjects affected / exposed	5 / 212 (2.36%)	4 / 210 (1.90%)	
occurrences (all)	5	4	
Hypotension			
subjects affected / exposed	4 / 212 (1.89%)	4 / 210 (1.90%)	
occurrences (all)	4	4	
Icterus			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	

Ileus				
subjects affected / exposed	10 / 212 (4.72%)	8 / 210 (3.81%)		
occurrences (all)	10	8		
Incisional hernia				
subjects affected / exposed	1 / 212 (0.47%)	1 / 210 (0.48%)		
occurrences (all)	1	1		
Increased bronchial secretion				
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)		
occurrences (all)	1	0		
Inguinal hernia				
subjects affected / exposed	1 / 212 (0.47%)	1 / 210 (0.48%)		
occurrences (all)	1	1		
Initial insomnia				
subjects affected / exposed	1 / 212 (0.47%)	2 / 210 (0.95%)		
occurrences (all)	1	2		
International normalised ratio increased				
subjects affected / exposed	1 / 212 (0.47%)	1 / 210 (0.48%)		
occurrences (all)	1	1		
Intestinal ischaemia				
subjects affected / exposed	2 / 212 (0.94%)	0 / 210 (0.00%)		
occurrences (all)	2	0		
Joint swelling				
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)		
occurrences (all)	0	1		
Laceration				
subjects affected / exposed	0 / 212 (0.00%)	3 / 210 (1.43%)		
occurrences (all)	0	3		
Lacrimation increased				
subjects affected / exposed	4 / 212 (1.89%)	0 / 210 (0.00%)		
occurrences (all)	4	0		
Lipase decreased				
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)		
occurrences (all)	1	0		
Lipase increased				

subjects affected / exposed	2 / 212 (0.94%)	2 / 210 (0.95%)	
occurrences (all)	2	2	
Malaise			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Memory impairment			
subjects affected / exposed	0 / 212 (0.00%)	2 / 210 (0.95%)	
occurrences (all)	0	2	
Mental disorder			
subjects affected / exposed	128 / 212 (60.38%)	123 / 210 (58.57%)	
occurrences (all)	128	123	
Microangiopathy			
subjects affected / exposed	0 / 212 (0.00%)	2 / 210 (0.95%)	
occurrences (all)	0	2	
Mucosal dryness			
subjects affected / exposed	1 / 212 (0.47%)	1 / 210 (0.48%)	
occurrences (all)	1	1	
Mucositis/Stomatitis			
subjects affected / exposed	64 / 212 (30.19%)	50 / 210 (23.81%)	
occurrences (all)	64	50	
Muscle spasms			
subjects affected / exposed	5 / 212 (2.36%)	6 / 210 (2.86%)	
occurrences (all)	5	6	
Muscular weakness			
subjects affected / exposed	1 / 212 (0.47%)	1 / 210 (0.48%)	
occurrences (all)	1	1	
Myopathy			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences (all)	0	1	
Myosclerosis			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Nail changes/Paronychia			
subjects affected / exposed	6 / 212 (2.83%)	11 / 210 (5.24%)	
occurrences (all)	6	11	
Nasal congestion			

subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences (all)	0	1	
Nasal discomfort			
subjects affected / exposed	1 / 212 (0.47%)	1 / 210 (0.48%)	
occurrences (all)	1	1	
Nasal dryness			
subjects affected / exposed	1 / 212 (0.47%)	6 / 210 (2.86%)	
occurrences (all)	1	6	
Nasal inflammation			
subjects affected / exposed	2 / 212 (0.94%)	1 / 210 (0.48%)	
occurrences (all)	2	1	
Nausea			
subjects affected / exposed	81 / 212 (38.21%)	103 / 210 (49.05%)	
occurrences (all)	81	103	
Neutropenic sepsis			
subjects affected / exposed	1 / 212 (0.47%)	1 / 210 (0.48%)	
occurrences (all)	1	1	
Night sweats			
subjects affected / exposed	2 / 212 (0.94%)	7 / 210 (3.33%)	
occurrences (all)	2	7	
Odynophagia			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Onycholysis			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Onychoclasis			
subjects affected / exposed	7 / 212 (3.30%)	5 / 210 (2.38%)	
occurrences (all)	7	5	
Onychomadesis			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences (all)	0	1	
Onychomycosis			
subjects affected / exposed	2 / 212 (0.94%)	3 / 210 (1.43%)	
occurrences (all)	2	3	
Osteonecrosis			

subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Other			
subjects affected / exposed	37 / 212 (17.45%)	25 / 210 (11.90%)	
occurrences (all)	37	25	
PCO2 decreased			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
PO2 decreased			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	125 / 212 (58.96%)	121 / 210 (57.62%)	
occurrences (all)	125	121	
Palpitations			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Performance status decreased			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences (all)	0	1	
Pleural effusion			
subjects affected / exposed	2 / 212 (0.94%)	1 / 210 (0.48%)	
occurrences (all)	2	1	
Pleurisy			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences (all)	0	1	
Pollakiuria			
subjects affected / exposed	0 / 212 (0.00%)	2 / 210 (0.95%)	
occurrences (all)	0	2	
Procedural site reaction			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences (all)	0	1	
Productive cough			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Prothrombin time prolonged			

subjects affected / exposed	2 / 212 (0.94%)	1 / 210 (0.48%)	
occurrences (all)	2	1	
Respiratory distress			
subjects affected / exposed	3 / 212 (1.42%)	2 / 210 (0.95%)	
occurrences (all)	3	2	
Rhinorrhoea			
subjects affected / exposed	3 / 212 (1.42%)	2 / 210 (0.95%)	
occurrences (all)	3	2	
Salivary hypersecretion			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences (all)	0	1	
Sjogren's syndrome			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Sleep apnoea syndrome			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Subileus			
subjects affected / exposed	1 / 212 (0.47%)	1 / 210 (0.48%)	
occurrences (all)	1	1	
Syncope			
subjects affected / exposed	2 / 212 (0.94%)	7 / 210 (3.33%)	
occurrences (all)	2	7	
Thirst			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences (all)	0	1	
Throat tightness			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Thyroid-dysregulation			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences (all)	0	1	
Tooth extraction			
subjects affected / exposed	2 / 212 (0.94%)	0 / 210 (0.00%)	
occurrences (all)	2	0	
Varicose vein			

subjects affected / exposed	0 / 212 (0.00%)	3 / 210 (1.43%)	
occurrences (all)	0	3	
Vertigo			
subjects affected / exposed	4 / 212 (1.89%)	1 / 210 (0.48%)	
occurrences (all)	4	1	
Vomiting			
subjects affected / exposed	35 / 212 (16.51%)	53 / 210 (25.24%)	
occurrences (all)	35	53	
Weight decreased			
subjects affected / exposed	21 / 212 (9.91%)	25 / 210 (11.90%)	
occurrences (all)	21	25	
Weight increased			
subjects affected / exposed	3 / 212 (1.42%)	6 / 210 (2.86%)	
occurrences (all)	3	6	
Withdrawal syndrome			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences (all)	0	1	
Immune system disorders			
Arthritis			
subjects affected / exposed	1 / 212 (0.47%)	1 / 210 (0.48%)	
occurrences (all)	1	1	
Chills			
subjects affected / exposed	5 / 212 (2.36%)	6 / 210 (2.86%)	
occurrences (all)	5	6	
Product issues			
Device dislocation			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Device related infection			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Infusional-related allergic reaction			
subjects affected / exposed	1 / 212 (0.47%)	2 / 210 (0.95%)	
occurrences (all)	1	2	
Medical device implantation			

subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Overdose			
subjects affected / exposed	1 / 212 (0.47%)	3 / 210 (1.43%)	
occurrences (all)	1	3	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Contusion			
subjects affected / exposed	3 / 212 (1.42%)	0 / 210 (0.00%)	
occurrences (all)	3	0	
Fall			
subjects affected / exposed	5 / 212 (2.36%)	3 / 210 (1.43%)	
occurrences (all)	5	3	
Femoral neck fracture			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Haematoma			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences (all)	0	1	
Hand fracture			
subjects affected / exposed	0 / 212 (0.00%)	2 / 210 (0.95%)	
occurrences (all)	0	2	
Rib fracture			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences (all)	0	1	
Sepsis			
subjects affected / exposed	1 / 212 (0.47%)	2 / 210 (0.95%)	
occurrences (all)	1	2	
Wound			
subjects affected / exposed	1 / 212 (0.47%)	2 / 210 (0.95%)	
occurrences (all)	1	2	
Wound healing complications			

subjects affected / exposed	5 / 212 (2.36%)	5 / 210 (2.38%)	
occurrences (all)	5	5	
Congenital, familial and genetic disorders			
Erectile dysfunction			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences (all)	0	1	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	7 / 212 (3.30%)	2 / 210 (0.95%)	
occurrences (all)	7	2	
Blood pressure increased			
subjects affected / exposed	4 / 212 (1.89%)	1 / 210 (0.48%)	
occurrences (all)	4	1	
Cardiac disorder			
subjects affected / exposed	2 / 212 (0.94%)	1 / 210 (0.48%)	
occurrences (all)	2	1	
Cardiac failure			
subjects affected / exposed	1 / 212 (0.47%)	2 / 210 (0.95%)	
occurrences (all)	1	2	
Cardiac toxicity			
subjects affected / exposed	13 / 212 (6.13%)	11 / 210 (5.24%)	
occurrences (all)	13	11	
Cardial-ischemic event			
subjects affected / exposed	3 / 212 (1.42%)	0 / 210 (0.00%)	
occurrences (all)	3	0	
Cardiomyopathy			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Cardiovascular disorder			
subjects affected / exposed	2 / 212 (0.94%)	4 / 210 (1.90%)	
occurrences (all)	2	4	
Cardiovascular insufficiency			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Circulatory collapse			

subjects affected / exposed	4 / 212 (1.89%)	2 / 210 (0.95%)	
occurrences (all)	4	2	
Tachycardia			
subjects affected / exposed	5 / 212 (2.36%)	3 / 210 (1.43%)	
occurrences (all)	5	3	
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences (all)	0	1	
Cholinergic syndrome			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences (all)	0	1	
Convulsion			
subjects affected / exposed	3 / 212 (1.42%)	0 / 210 (0.00%)	
occurrences (all)	3	0	
Disturbance in attention			
subjects affected / exposed	0 / 212 (0.00%)	4 / 210 (1.90%)	
occurrences (all)	0	4	
Nervous system disorder			
subjects affected / exposed	27 / 212 (12.74%)	18 / 210 (8.57%)	
occurrences (all)	27	18	
Neurological disorder			
subjects affected / exposed	5 / 212 (2.36%)	3 / 210 (1.43%)	
occurrences (all)	5	3	
PNP			
subjects affected / exposed	27 / 212 (12.74%)	18 / 210 (8.57%)	
occurrences (all)	27	18	
Tremor			
subjects affected / exposed	0 / 212 (0.00%)	2 / 210 (0.95%)	
occurrences (all)	0	2	
Blood and lymphatic system disorders			
Abscess limb			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Abscesses fistulae			

subjects affected / exposed	7 / 212 (3.30%)	7 / 210 (3.33%)	
occurrences (all)	7	7	
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Activated partial thromboplastin time shortened			
subjects affected / exposed	16 / 212 (7.55%)	13 / 210 (6.19%)	
occurrences (all)	16	13	
Ascites			
subjects affected / exposed	3 / 212 (1.42%)	1 / 210 (0.48%)	
occurrences (all)	3	1	
Bleeding/hemorrhage			
subjects affected / exposed	2 / 212 (0.94%)	6 / 210 (2.86%)	
occurrences (all)	2	6	
Blood albumin decreased			
subjects affected / exposed	2 / 212 (0.94%)	6 / 210 (2.86%)	
occurrences (all)	2	6	
Blood bicarbonate decreased			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Blood creatinine decreased			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences (all)	0	1	
Blood creatinine increased			
subjects affected / exposed	31 / 212 (14.62%)	27 / 210 (12.86%)	
occurrences (all)	31	27	
Blood glucose increased			
subjects affected / exposed	2 / 212 (0.94%)	1 / 210 (0.48%)	
occurrences (all)	2	1	
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences (all)	0	1	
Blood uric acid increased			

subjects affected / exposed	5 / 212 (2.36%)	5 / 210 (2.38%)	
occurrences (all)	5	5	
Blood urine present			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Coagulation time prolonged			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences (all)	0	1	
Electrolyte imbalance			
subjects affected / exposed	27 / 212 (12.74%)	27 / 210 (12.86%)	
occurrences (all)	27	27	
Febrile neutropenia			
subjects affected / exposed	3 / 212 (1.42%)	3 / 210 (1.43%)	
occurrences (all)	3	3	
Haematologic toxicity			
subjects affected / exposed	147 / 212 (69.34%)	161 / 210 (76.67%)	
occurrences (all)	147	161	
Hyperalbuminaemia			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences (all)	0	1	
Iron deficiency			
subjects affected / exposed	1 / 212 (0.47%)	1 / 210 (0.48%)	
occurrences (all)	1	1	
Leukocytosis			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Leukopenia			
subjects affected / exposed	0 / 212 (0.00%)	2 / 210 (0.95%)	
occurrences (all)	0	2	
Lymphopenia			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Neutropenia			
subjects affected / exposed	0 / 212 (0.00%)	2 / 210 (0.95%)	
occurrences (all)	0	2	
Oedema			

subjects affected / exposed	26 / 212 (12.26%)	23 / 210 (10.95%)	
occurrences (all)	26	23	
Protein total decreased			
subjects affected / exposed	6 / 212 (2.83%)	8 / 210 (3.81%)	
occurrences (all)	6	8	
Proteinuria			
subjects affected / exposed	8 / 212 (3.77%)	10 / 210 (4.76%)	
occurrences (all)	8	10	
Thrombocytopenia			
subjects affected / exposed	2 / 212 (0.94%)	1 / 210 (0.48%)	
occurrences (all)	2	1	
Thromboembolic event			
subjects affected / exposed	37 / 212 (17.45%)	33 / 210 (15.71%)	
occurrences (all)	37	33	
Thrombosis (any)			
subjects affected / exposed	5 / 212 (2.36%)	5 / 210 (2.38%)	
occurrences (all)	5	5	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 212 (0.00%)	2 / 210 (0.95%)	
occurrences (all)	0	2	
Chromatopsia			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Eye irritation			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Ocular hyperaemia			
subjects affected / exposed	2 / 212 (0.94%)	0 / 210 (0.00%)	
occurrences (all)	2	0	
Photophobia			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences (all)	0	1	
Retinal detachment			
subjects affected / exposed	1 / 212 (0.47%)	1 / 210 (0.48%)	
occurrences (all)	1	1	

Vision blurred			
subjects affected / exposed	1 / 212 (0.47%)	1 / 210 (0.48%)	
occurrences (all)	1	1	
Visual impairment			
subjects affected / exposed	5 / 212 (2.36%)	1 / 210 (0.48%)	
occurrences (all)	5	1	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	3 / 212 (1.42%)	10 / 210 (4.76%)	
occurrences (all)	3	10	
Abdominal hernia			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences (all)	0	1	
Anal haemorrhage			
subjects affected / exposed	2 / 212 (0.94%)	0 / 210 (0.00%)	
occurrences (all)	2	0	
Anorectal discomfort			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences (all)	0	1	
Cholangitis			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Cholelithiasis			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Cholestasis			
subjects affected / exposed	1 / 212 (0.47%)	2 / 210 (0.95%)	
occurrences (all)	1	2	
Constipation			
subjects affected / exposed	28 / 212 (13.21%)	46 / 210 (21.90%)	
occurrences (all)	28	46	
Diarrhoea			
subjects affected / exposed	111 / 212 (52.36%)	124 / 210 (59.05%)	
occurrences (all)	111	124	
GI perforation			

subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences (all)	0	1	
Gastritis			
subjects affected / exposed	1 / 212 (0.47%)	1 / 210 (0.48%)	
occurrences (all)	1	1	
Gastrointestinal disorder			
subjects affected / exposed	2 / 212 (0.94%)	2 / 210 (0.95%)	
occurrences (all)	2	2	
Gastrointestinal perforation			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences (all)	0	1	
Gastrointestinal ulcer			
subjects affected / exposed	1 / 212 (0.47%)	1 / 210 (0.48%)	
occurrences (all)	1	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Hepatologic toxicity			
subjects affected / exposed	128 / 212 (60.38%)	123 / 210 (58.57%)	
occurrences (all)	128	123	
Skin and subcutaneous tissue disorders			
Acneiform exanthema/Rash			
subjects affected / exposed	16 / 212 (7.55%)	13 / 210 (6.19%)	
occurrences (all)	16	13	
Skin disorder			
subjects affected / exposed	5 / 212 (2.36%)	3 / 210 (1.43%)	
occurrences (all)	5	3	
Skin reaction			
subjects affected / exposed	58 / 212 (27.36%)	59 / 210 (28.10%)	
occurrences (all)	58	59	
Renal and urinary disorders			

Bladder discomfort			
subjects affected / exposed	6 / 212 (2.83%)	5 / 210 (2.38%)	
occurrences (all)	6	5	
Calculus ureteric			
subjects affected / exposed	2 / 212 (0.94%)	0 / 210 (0.00%)	
occurrences (all)	2	0	
Nitrite urine			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Renal disorder			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Renal failure			
subjects affected / exposed	2 / 212 (0.94%)	5 / 210 (2.38%)	
occurrences (all)	2	5	
Urinary hesitation			
subjects affected / exposed	1 / 212 (0.47%)	1 / 210 (0.48%)	
occurrences (all)	1	1	
Urinary retention			
subjects affected / exposed	0 / 212 (0.00%)	1 / 210 (0.48%)	
occurrences (all)	0	1	
Urinary tract disorder			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Endocrine disorder			
subjects affected / exposed	1 / 212 (0.47%)	1 / 210 (0.48%)	
occurrences (all)	1	1	
Infections and infestations			
Febrile infection			
subjects affected / exposed	1 / 212 (0.47%)	0 / 210 (0.00%)	
occurrences (all)	1	0	
Fever			
subjects affected / exposed	24 / 212 (11.32%)	38 / 210 (18.10%)	
occurrences (all)	24	38	
Infection			

subjects affected / exposed occurrences (all)	102 / 212 (48.11%) 102	102 / 210 (48.57%) 102	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 July 2010	To evaluate the tumor dynamics in all study patients, it is planned that too the follow-up examinations (every 3 months for a minimum of 36 Months after randomization) a computed tomography and a RECIST-compliant one Assessment of this carried out according to the RECIST criteria version 1.1 become. According to this amendment, these should be mandatory until the first one is established definitive progression (arm A) or the second definitive progression (arm B) respectively. Furthermore, instead of 10ml EDTA blood now 10ml PAXgene blood once at the start of the study therapy (or within the first two treatment cycles). All samples are, as described in the existing test plan in version 2.0 from 25.08.2010, sent to the central biobank at Klinikum Großhadern. In addition, this amendment indicates that the Responsibility for the area of data management from the company "Scientific Service Pharma (WiSP) GmbH" to ClinAssess GmbH and that editorial changes were made throughout the test plan have been carried out (see also the test plan version 3.0 dated May 19, 2011 with highlighted changes). As part of this amendment, the study title was also modified, since the Existing study titles are not comprehensive and sufficiently precise Treatment options reflected within the study. The modified one According to the sequential (de) escalation options (the less intensive therapy arm (A) offers the possibility of escalation (after Progression), the more intensive therapy arm (B) offers the possibility of de-escalation (in the case of a stable disease state or toxicity) and can subsequently be re-escalated again (according to progression)) calculation.
08 February 2013	changes in the Formulation for study therapy made. It was the one so far existing formulation "Capecitabin" around the term "FUFA" (5-fluorouracil and Folinic acid), or the formulation "XELIRI" (capecitabine plus irinotecan) around the Term “FOLFIRI” (5-fluorouracil, folinic acid and irinotecan) added. A detailed All changes to this are not listed. As a result of the opening of the study to the infusional fluoropyrimidine was a further secondary study endpoint formulated, as well as the inclusion and exclusion criteria customized. The primary and secondary study objectives were for the better Understanding editorially revised but the content remains unchanged. Since the study with this amendment after the approval extension for Bevacizumab for “treatment beyond progression” will be continued as soon as it comes into force of this amendment Bevacizumab is no longer made available as study product. Corresponding changes were made in the test plan. The other changes in the test plan with regard to the translational Research project can be found listed in this amendment. In addition, this amendment indicates that responsibility for the field of biometrics and statistics from the company "Wissenschaftlicher Service Pharma (WiSP) GmbH ”was transferred to ClinAssess GmbH.

09 June 2015	The present change to the study plan of the ML22011 / AIOKRK0110 study is addressed editorial changes, updating of side effects, adding new ones secondary endpoints (e.g. risk group evaluation, co-morbidity, central, pseudonymized collection and evaluation of the CT images), as well as a reduction in Sample size planning. The current design sees the non-inferiority of the "time-to-failure" as the primary endpoint. of-strategy "(= TFS) from ARM A to ARM B. Although the sequential Therapy of metastatic colorectal cancer according to the current ESMO guideline as Therapy option and therefore the comparison of a sequence and an up-front Therapy appears interesting and necessary, in our view the primary endpoint is im current scientific context of the study is not unproblematic, as we have already done in Discussed in detail at the joint ethics committee meeting in April 2015 to have. After a detailed (including statistical) consultation with you, we will apply for this Amendments propose a reduction in power from 80% to 70%: This means a Case number reduction from 506 evaluable patients to 378 evaluable patients and thus an estimated total enrollment of 420-450 patients, depending on the proportion of evaluable patients. This goal is at an average recruitment of 7-8 Patients per month and a number of patients of 396 (as of June 8, 2015) by the end of 2015 very high probability achievable. This solution leaves the study with enough sample size to answering the primary hierarchically tested hypothesis and is also a good basis to evaluate the secondary endpoints (such as PFS, OS and molecular markers) in the Within a timely justifiable process.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30388045