



Clinical trial results:

A Phase 2, Open Label, Multicenter, Randomized Trial Comparing Tivozanib in Combination with mFOLFOX6 with Bevacizumab in Combination with mFOLFOX6 in Stage IV Metastatic Colorectal Cancer (mCRC) Subjects

Summary

EudraCT number	2011-003502-24
Trial protocol	BE GB CZ ES AT HU FI NL IT
Global end of trial date	07 January 2015

Results information

Result version number	v1 (current)
This version publication date	05 April 2016
First version publication date	07 March 2015

Trial information

Trial identification

Sponsor protocol code	4130-CL-0201
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01478594
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Global Development, Inc.
Sponsor organisation address	1 Astellas Way, Northbrook, United States, 60062
Public contact	Clinical Trial Disclosure, Astellas Pharma Global Development, Inc., Astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Disclosure, Astellas Pharma Global Development, Inc., Astellas.resultsdisclosure@astellas.com

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 February 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 February 2014
Global end of trial reached?	Yes
Global end of trial date	07 January 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To compare progression-free survival (PFS) between tivozanib in combination with mFOLFOX6 with bevacizumab in combination with mFOLFOX6 based on investigator radiological tumor assessment.

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, ICH GCP Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki.

Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal and/or regional legislation related to the privacy and protection of personal information.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 December 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Spain: 30
Country: Number of subjects enrolled	United Kingdom: 26
Country: Number of subjects enrolled	Austria: 11
Country: Number of subjects enrolled	Belgium: 19
Country: Number of subjects enrolled	Czech Republic: 21
Country: Number of subjects enrolled	Finland: 6
Country: Number of subjects enrolled	Hungary: 32
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Australia: 24
Country: Number of subjects enrolled	Canada: 17
Country: Number of subjects enrolled	United States: 70

Worldwide total number of subjects	265
EEA total number of subjects	154

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)	149
From 65 to 84 years	116
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were at least 18 years of age with Stage IV metastatic colorectal cancer (mCRC) and measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (Version 1.1).

Participants who completed are participants still on study as of 28 February 2014.

Pre-assignment

Screening details:

Participants were to be randomized in a 2:1 ratio (estimated 168 patients in the Tivozanib+mFOLFOX6 arm and estimated 84 patients in the Bevacizumab+mFOLFOX6 arm) and stratified by: Lactate Dehydrogenase (LDH) status ($< 1.5 \times$ the upper limit of normal [ULN] or $> 1.5 \times$ ULN), origin of cancer (rectal or colon), number of metastatic sites (1 or ≥ 2).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Tivozanib + mFOLFOX6

Arm description:

Participants received 1.5 mg tivozanib orally once daily beginning on Day 1 of each cycle for 21 days followed by 7 days off treatment. Participants also received mFOLFOX6 chemotherapy every 2 weeks on Days 1 and 15 of each cycle.

Arm type	Experimental
Investigational medicinal product name	Tivozanib
Investigational medicinal product code	ASP4130
Other name	Tivozanib Hydrochloride
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received 1.5 mg of tivozanib orally once daily beginning on day 1 of each cycle for 21 days followed by 7 days off treatment. On days when patients received both tivozanib and mFOLFOX6, tivozanib was to be administered at least 1 hour prior to the start of the mFOLFOX6 chemotherapy regimen or per institutional guidelines.

Investigational medicinal product name	mFOLFOX6
Investigational medicinal product code	
Other name	modified FOLFOX-6
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous bolus use , Intravenous use

Dosage and administration details:

mFOLFOX6 is the sixth variation of a combination chemotherapy regimen consisting of folinic acid (leucovorin), fluorouracil and oxaliplatin (Oxaliplatin: days 1 and 15, 85 mg/m² intravenous bolus in 500 mL of 5% dextrose in water (D5W) over 2 hours; Leucovorin calcium: days 1 and 15, 400 mg/m² intravenous bolus in 500 mL of D5W over 2 hours (could have been given concurrently with oxaliplatin through a separate intravenous line; Fluorouracil bolus: days 1 and 15, 400 mg/m² intravenous bolus over 5 to 15 minutes; Fluorouracil infusion: days 1 to 3 and 15 to 17, 2400 mg/m² continuous intravenous infusion via infusion pump over 46 hours). Participants received mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Arm title	Bevacizumab + mFOLFOX6
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Arm description:

Participants received 5 mg/kg bevacizumab via intravenous infusion every 2 weeks on Days 1 and 15 of each cycle and mFOLFOX6 chemotherapy every 2 weeks on Days 1 and 15 of each cycle.

Arm type	Active comparator
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received a dose of 5 mg/kg bevacizumab via intravenous infusion every 2 weeks on days 1 and 15 of each cycle. Bevacizumab was to be administered prior to the start of the mFOLFOX6 chemotherapy regimen or per institution guidelines.

Investigational medicinal product name	mFOLFOX6
Investigational medicinal product code	
Other name	modified FOLFOX-6
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous bolus use , Intravenous use

Dosage and administration details:

mFOLFOX6 is the sixth variation of a combination chemotherapy regimen consisting of folinic acid (leucovorin), fluorouracil and oxaliplatin (Oxaliplatin: days 1 and 15, 85 mg/m² intravenous bolus in 500 mL of 5% dextrose in water (D5W) over 2 hours; Leucovorin calcium: days 1 and 15, 400 mg/m² intravenous bolus in 500 mL of D5W over 2 hours (could have been given concurrently with oxaliplatin through a separate intravenous line; Fluorouracil bolus: days 1 and 15, 400 mg/m² intravenous bolus over 5 to 15 minutes; Fluorouracil infusion: days 1 to 3 and 15 to 17, 2400 mg/m² continuous intravenous infusion via infusion pump over 46 hours). Participants received mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Number of subjects in period 1	Tivozanib + mFOLFOX6	Bevacizumab + mFOLFOX6
Started	177	88
Received treatment	177	87
Completed	112	60
Not completed	65	28
Randomized but never received study drug	-	1
Consent withdrawn by subject	9	3
Death	45	18
Study terminated by sponsor	8	5
Lost to follow-up	3	1

Baseline characteristics

Reporting groups

Reporting group title	Tivozanib + mFOLFOX6
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Reporting group description:

Participants received 1.5 mg tivozanib orally once daily beginning on Day 1 of each cycle for 21 days followed by 7 days off treatment. Participants also received mFOLFOX6 chemotherapy every 2 weeks on Days 1 and 15 of each cycle.

Reporting group title	Bevacizumab + mFOLFOX6
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Reporting group description:

Participants received 5 mg/kg bevacizumab via intravenous infusion every 2 weeks on Days 1 and 15 of each cycle and mFOLFOX6 chemotherapy every 2 weeks on Days 1 and 15 of each cycle.

Reporting group values	Tivozanib + mFOLFOX6	Bevacizumab + mFOLFOX6	Total
Number of subjects	177	88	265
Age categorical			
Units: Subjects			
< 65 years	101	48	149
≥ 65 years	76	40	116
Age continuous			
Units: years			
arithmetic mean	61.9	62.6	
standard deviation	± 9.58	± 11.17	-
Gender categorical			
Units: Subjects			
Female	59	33	92
Male	118	55	173
Race			
Units: Subjects			
White	169	85	254
Black or African American	2	0	2
Asian	3	2	5
Native Hawaiian or other Pacific Islander	1	1	2
Other	2	0	2
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	170	86	256
Hispanic or Latino	6	2	8
Unknown or Not reported	1	0	1
ECOG performance status			
Eastern Cooperative Oncology Group (ECOG); ECOG criteria: 0: Fully active. 1: Ambulatory, carry out work of a light or sedentary nature. 2: Ambulatory, capable of all self-care. 3: Capable of limited self-care, confined to bed or chair more than 50% of waking hours. 4: Completely disabled, no self-care, totally confined to bed or chair. 5: Dead.			
Units: Subjects			
ECOG=0	95	58	153
ECOG=1	82	30	112
ECOG=2	0	0	0
ECOG=3	0	0	0

ECOG=4	0	0	0
ECOG=5	0	0	0
LDH Status			
Lactate dehydrogenase (LDH); The upper limit of normal (ULN) from the site was used.			
Units: Subjects			
< 1.5 x ULN	127	64	191
≥ 1.5 x ULN	50	24	74
Origin of Cancer			
Units: Subjects			
Rectal	53	24	77
Colon	124	64	188
Number of metastatic sites/organs			
Units: Subjects			
One (1)	56	30	86
Two (2)	80	34	114
Three (3)	29	21	50
≥ Four (4)	12	3	15
KRAS Mutation Status			
Kirsten rat sarcoma (KRAS)			
Units: Subjects			
Wild-type	33	21	54
Mutant	23	16	39
Unknown	121	51	172
Time since initial diagnosis			
Units: months			
arithmetic mean	9.41	10.88	
standard deviation	± 20.473	± 21.055	-
Number of metastatic sites at screening			
Units: metastatic sites			
arithmetic mean	2	2	
standard deviation	± 1.02	± 0.85	-

End points

End points reporting groups

Reporting group title	Tivozanib + mFOLFOX6
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Reporting group description:

Participants received 1.5 mg tivozanib orally once daily beginning on Day 1 of each cycle for 21 days followed by 7 days off treatment. Participants also received mFOLFOX6 chemotherapy every 2 weeks on Days 1 and 15 of each cycle.

Reporting group title	Bevacizumab + mFOLFOX6
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Reporting group description:

Participants received 5 mg/kg bevacizumab via intravenous infusion every 2 weeks on Days 1 and 15 of each cycle and mFOLFOX6 chemotherapy every 2 weeks on Days 1 and 15 of each cycle.

Subject analysis set title	Tivozanib + mFOLFOX6: LDH < 1.5 ULN
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Subject analysis set type	Full analysis
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Subject analysis set description:

Participants with Lactate Dehydrogenase (LDH) < 1.5 ULN received 1.5 mg of tivozanib orally once daily beginning on day 1 of each cycle for 21 days followed by 7 days off treatment and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Subject analysis set title	Bevacizumab + mFOLFOX6: LDH < 1.5 ULN
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Subject analysis set type	Full analysis
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Subject analysis set description:

Participants with LDH < 1.5 ULN received a dose of 5 mg/kg bevacizumab via intravenous infusion every 2 weeks on days 1 and 15 of each cycle and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Subject analysis set title	Tivozanib + mFOLFOX6: LDH ≥ 1.5 ULN
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Subject analysis set type	Full analysis
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Subject analysis set description:

Participants with LDH ≥ 1.5 ULN received 1.5 mg of tivozanib orally once daily beginning on day 1 of each cycle for 21 days followed by 7 days off treatment and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Subject analysis set title	Bevacizumab + mFOLFOX6: LDH ≥ 1.5 ULN
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Subject analysis set type	Full analysis
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Subject analysis set description:

Participants with LDH ≥ 1.5 ULN received a dose of 5 mg/kg bevacizumab via intravenous infusion every 2 weeks on days 1 and 15 of each cycle and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Subject analysis set title	Tivozanib + mFOLFOX6: VEGF-A < Median
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Subject analysis set type	Full analysis
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Subject analysis set description:

Participants with Vascular Endothelial Growth Factor-A (VEGF-A) < median received 1.5 mg of tivozanib orally once daily beginning on day 1 of each cycle for 21 days followed by 7 days off treatment and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with serum samples available.

Subject analysis set title	Bevacizumab + mFOLFOX: VEGF-A < Median
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Subject analysis set type	Full analysis
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Subject analysis set description:

Participants with VEGF-A < median received a dose of 5 mg/kg bevacizumab via intravenous infusion every 2 weeks on days 1 and 15 of each cycle and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with serum samples available.

Subject analysis set title	Tivozanib + mFOLFOX6: VEGF-A ≥ Median
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Subject analysis set type	Full analysis
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Subject analysis set description:

Participants with VEGF-A ≥ median received 1.5 mg of tivozanib orally once daily beginning on day 1 of

each cycle for 21 days followed by 7 days off treatment and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with serum samples available.

Subject analysis set title	Bevacizumab + mFOLFOX: VEGF-A \geq Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with VEGF-A \geq median received a dose of 5 mg/kg bevacizumab via intravenous infusion every 2 weeks on days 1 and 15 of each cycle and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with serum samples available.

Subject analysis set title	Tivozanib + mFOLFOX6: VEGF-C < Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with Vascular Endothelial Growth Factor-C (VEGF-C) < median received 1.5 mg of tivozanib orally once daily beginning on day 1 of each cycle for 21 days followed by 7 days off treatment and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with serum samples available.

Subject analysis set title	Bevacizumab + mFOLFOX6: VEGF-C < Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with VEGF-C < median received a dose of 5 mg/kg bevacizumab via intravenous infusion every 2 weeks on days 1 and 15 of each cycle and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with serum samples available.

Subject analysis set title	Tivozanib + mFOLFOX6: VEGF-C \geq Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with VEGF-C \geq median received 1.5 mg of tivozanib orally once daily beginning on day 1 of each cycle for 21 days followed by 7 days off treatment and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with serum samples available.

Subject analysis set title	Bevacizumab + mFOLFOX6: VEGF-C \geq Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with VEGF-C \geq median received a dose of 5 mg/kg bevacizumab via intravenous infusion every 2 weeks on days 1 and 15 of each cycle and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with serum samples available.

Subject analysis set title	Tivozanib + mFOLFOX6: VEGF-C/VEGF-A < Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with VEGF-C/VEGF-A < median received 1.5 mg of tivozanib orally once daily beginning on day 1 of each cycle for 21 days followed by 7 days off treatment and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with serum samples available.

Subject analysis set title	Bevacizumab + mFOLFOX6: VEGF-C/VEGF-A < Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with VEGF-C/VEGF-A < median received a dose of 5 mg/kg bevacizumab via intravenous infusion every 2 weeks on days 1 and 15 of each cycle and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with serum samples available.

Subject analysis set title	Tivozanib + mFOLFOX6: VEGF-C/VEGF-A \geq Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with VEGF-C/VEGF-A \geq median received 1.5 mg of tivozanib orally once daily beginning on day 1 of each cycle for 21 days followed by 7 days off treatment and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with serum samples available.

Subject analysis set title	Bevacizumab + mFOLFOX6: VEGF-C/VEGF-A \geq Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with VEGF-C/VEGF-A \geq median received a dose of 5 mg/kg bevacizumab via intravenous infusion every 2 weeks on days 1 and 15 of each cycle and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with serum samples available.

Subject analysis set title	Tivozanib + mFOLFOX6: sVEGFR-2 < Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with Soluble Vascular Endothelial Growth Factor Receptor-2 (sVEGFR-2) < median received 1.5 mg of tivozanib orally once daily beginning on day 1 of each cycle for 21 days followed by 7 days off treatment and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with serum samples available.

Subject analysis set title	Bevacizumab + mFOLFOX6: sVEGFR-2 < Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with sVEGFR-2 < median received a dose of 5 mg/kg bevacizumab via intravenous infusion every 2 weeks on days 1 and 15 of each cycle and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with serum samples available.

Subject analysis set title	Tivozanib + mFOLFOX6: sVEGFR-2 \geq Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with sVEGFR-2 \geq median received 1.5 mg of tivozanib orally once daily beginning on day 1 of each cycle for 21 days followed by 7 days off treatment and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with serum samples available.

Subject analysis set title	Bevacizumab + mFOLFOX6: sVEGFR-2 \geq Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with sVEGFR-2 \geq median received a dose of 5 mg/kg bevacizumab via intravenous infusion every 2 weeks on days 1 and 15 of each cycle and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with serum samples available.

Subject analysis set title	Tivozanib + mFOLFOX6: sVEGFR-3 < Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with Soluble Vascular Endothelial Growth Factor Receptor-3 (sVEGFR-3) < median received 1.5 mg of tivozanib orally once daily beginning on day 1 of each cycle for 21 days followed by 7 days off treatment and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with serum samples available.

Subject analysis set title	Bevacizumab + mFOLFOX6: sVEGFR-3 < Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with sVEGFR-3 < median received a dose of 5 mg/kg bevacizumab via intravenous infusion every 2 weeks on days 1 and 15 of each cycle and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with serum samples available.

Subject analysis set title	Tivozanib + mFOLFOX6: sVEGFR-3 \geq Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with sVEGFR-3 \geq median received 1.5 mg of tivozanib orally once daily beginning on day 1 of each cycle for 21 days followed by 7 days off treatment and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with serum samples available.

Subject analysis set title	Bevacizumab + mFOLFOX6: sVEGFR-3 \geq Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with sVEGFR-3 \geq median received a dose of 5 mg/kg bevacizumab via intravenous infusion every 2 weeks on days 1 and 15 of each cycle and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with serum samples available.

Subject analysis set title	Tivozanib + mFOLFOX6: IL-8 < Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with Interleukin-8 (IL-8) < median received 1.5 mg of tivozanib orally once daily beginning on day 1 of each cycle for 21 days followed by 7 days off treatment and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with serum samples available.

Subject analysis set title	Bevacizumab + mFOLFOX6: IL-8 < Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with IL-8 < median received a dose of 5 mg/kg bevacizumab via intravenous infusion every 2 weeks on days 1 and 15 of each cycle and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with serum samples available.

Subject analysis set title	Tivozanib + mFOLFOX6: IL-8 \geq Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with IL-8 \geq median received 1.5 mg of tivozanib orally once daily beginning on day 1 of each cycle for 21 days followed by 7 days off treatment and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with serum samples available.

Subject analysis set title	Bevacizumab + mFOLFOX6: IL-8 \geq Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with IL-8 \geq median received a dose of 5 mg/kg bevacizumab via intravenous infusion every 2 weeks on days 1 and 15 of each cycle and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with serum samples available.

Subject analysis set title	Tivozanib + mFOLFOX6: Neuropilin < Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with Neuropilin < median received 1.5 mg of tivozanib orally once daily beginning on day 1 of each cycle for 21 days followed by 7 days off treatment and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

15 of each treatment cycle.

Analysis population as FAS with serum samples available.

Subject analysis set title	Bevacizumab + mFOLFOX6: Neuropilin < Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with Neuropilin < median received 1.5 mg of tivozanib orally once daily beginning on day 1 of each cycle for 21 days followed by 7 days off treatment and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with serum samples available.

Subject analysis set title	Tivozanib + MFOLFOX6: Neuropilin ≥ Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with Neuropilin ≥ median received 1.5 mg of tivozanib orally once daily beginning on day 1 of each cycle for 21 days followed by 7 days off treatment and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with serum samples available.

Subject analysis set title	Bevacizumab + mFOLFOX6: Neuropilin ≥ Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with Neuropilin ≥ median received a dose of 5 mg/kg bevacizumab via intravenous infusion every 2 weeks on days 1 and 15 of each cycle and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with serum samples available.

Subject analysis set title	Tivozanib + mFOLFOX6: VEGF-A RNA < Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with tumor VEGF-A Ribonucleic Acid (RNA) < median received 1.5 mg of tivozanib orally once daily beginning on day 1 of each cycle for 21 days followed by 7 days off treatment and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with tumor biopsy RNA samples available.

Subject analysis set title	Bevacizumab + mFOLFOX: VEGF-A RNA < Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with tumor VEGF-A RNA < median received a dose of 5 mg/kg bevacizumab via intravenous infusion every 2 weeks on days 1 and 15 of each cycle and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with tumor biopsy RNA samples available.

Subject analysis set title	Tivozanib + mFOLFOX6: VEGF-A RNA ≥ Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with tumor VEGF-A RNA ≥ median received 1.5 mg of tivozanib orally once daily beginning on day 1 of each cycle for 21 days followed by 7 days off treatment and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with tumor biopsy RNA samples available.

Subject analysis set title	Bevacizumab + mFOLFOX: VEGF-A RNA ≥ Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with tumor VEGF-A RNA ≥ median received a dose of 5 mg/kg bevacizumab via intravenous infusion every 2 weeks on days 1 and 15 of each cycle and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with tumor biopsy RNA samples available.

Subject analysis set title	Tivozanib + mFOLFOX6: VEGF-C RNA < Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with tumor VEGF-C RNA < median received 1.5 mg of tivozanib orally once daily beginning on day 1 of each cycle for 21 days followed by 7 days off treatment and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with tumor biopsy RNA samples available.

Subject analysis set title	Bevacizumab + mFOLFOX: VEGF-C RNA < Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with tumor VEGF-C RNA < median received a dose of 5 mg/kg bevacizumab via intravenous infusion every 2 weeks on days 1 and 15 of each cycle and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with tumor biopsy RNA samples available.

Subject analysis set title	Tivozanib + mFOLFOX6: VEGF-C RNA ≥ Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with tumor VEGF-C RNA ≥ median received 1.5 mg of tivozanib orally once daily beginning on day 1 of each cycle for 21 days followed by 7 days off treatment and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with tumor biopsy RNA samples available.

Subject analysis set title	Bevacizumab + mFOLFOX: VEGF-C RNA ≥ Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with tumor VEGF-C RNA ≥ median received a dose of 5 mg/kg bevacizumab via intravenous infusion every 2 weeks on days 1 and 15 of each cycle and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with tumor biopsy RNA samples available.

Subject analysis set title	Tivozanib + mFOLFOX6: VEGF-C/VEGF-A RNA < Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with tumor VEGF-C/VEGF-A RNA < median received 1.5 mg of tivozanib orally once daily beginning on day 1 of each cycle for 21 days followed by 7 days off treatment and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with tumor biopsy RNA samples available.

Subject analysis set title	Bevacizumab + mFOLFOX6: VEGF-C/VEGF-A RNA < Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with tumor VEGF-C/VEGF-A < median received a dose of 5 mg/kg bevacizumab via intravenous infusion every 2 weeks on days 1 and 15 of each cycle and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with tumor biopsy RNA samples available.

Subject analysis set title	Tivozanib + mFOLFOX6: VEGF-C/VEGF-A RNA ≥ Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with tumor VEGF-C/VEGF-A RNA ≥ median received 1.5 mg of tivozanib orally once daily beginning on day 1 of each cycle for 21 days followed by 7 days off treatment and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with tumor biopsy RNA samples available.

Subject analysis set title	Bevacizumab + mFOLFOX6: VEGF-C/VEGF-A RNA ≥ Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with tumor VEGF-C/VEGF-A RNA \geq median received a dose of 5 mg/kg bevacizumab via intravenous infusion every 2 weeks on days 1 and 15 of each cycle and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with tumor biopsy RNA samples available.

Subject analysis set title	Tivozanib + mFOLFOX6: VEGF-D RNA < Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with tumor Vascular Endothelial Growth Factor-D (VEGF-D) RNA < median received 1.5 mg of tivozanib orally once daily beginning on day 1 of each cycle for 21 days followed by 7 days off treatment and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with tumor biopsy RNA samples available.

Subject analysis set title	Bevacizumab + mFOLFOX: VEGF-D RNA < Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with tumor VEGF-D RNA < median received a dose of 5 mg/kg bevacizumab via intravenous infusion every 2 weeks on days 1 and 15 of each cycle and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with tumor biopsy RNA samples available.

Subject analysis set title	Tivozanib + mFOLFOX6: VEGF-D RNA \geq Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with tumor VEGF-D RNA \geq median received 1.5 mg of tivozanib orally once daily beginning on day 1 of each cycle for 21 days followed by 7 days off treatment and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with tumor biopsy RNA samples available.

Subject analysis set title	Bevacizumab + mFOLFOX: VEGF-D RNA \geq Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with tumor VEGF-D RNA \geq median received a dose of 5 mg/kg bevacizumab via intravenous infusion every 2 weeks on days 1 and 15 of each cycle and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with tumor biopsy RNA samples available.

Subject analysis set title	Tivozanib + mFOLFOX6: PIGF RNA < Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with tumor Placental Growth Factor (PIGF) RNA < median received 1.5 mg of tivozanib orally once daily beginning on day 1 of each cycle for 21 days followed by 7 days off treatment and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with tumor biopsy RNA samples available.

Subject analysis set title	Bevacizumab + mFOLFOX: PIGF RNA < Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with tumor PIGF RNA < median received a dose of 5 mg/kg bevacizumab via intravenous infusion every 2 weeks on days 1 and 15 of each cycle and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with tumor biopsy RNA samples available.

Subject analysis set title	Tivozanib + mFOLFOX6: PIGF RNA \geq Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with tumor PIGF RNA \geq median received 1.5 mg of tivozanib orally once daily beginning on day 1 of each cycle for 21 days followed by 7 days off treatment and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with tumor biopsy RNA samples available.

Subject analysis set title	Bevacizumab + mFOLFOX: PIGF RNA \geq Median
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with tumor PIGF RNA \geq median received a dose of 5 mg/kg bevacizumab via intravenous infusion every 2 weeks on days 1 and 15 of each cycle and mFOLFOX6 every 2 weeks on days 1 and 15 of each treatment cycle.

Analysis population as FAS with tumor biopsy RNA samples available.

Primary: Investigator-assessed Progression-Free Survival (PFS)

End point title	Investigator-assessed Progression-Free Survival (PFS)
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End point description:

The time from the date of randomization until objective tumor progression or death due to any cause. Objective tumor progression was determined through radiological imaging and based on the requirements of the Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1):

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study and an absolute increase of at least 5 mm, or unequivocal progression of existing non-target lesions or the appearance of one or more new lesions.

Participants who did not progress or had not died at the time of the analysis were censored at the date of last tumor assessment where non-progression was documented.

The analysis population is the Full Analysis Set (FAS), which included all randomized patients.

End point type	Primary
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End point timeframe:

From randomization until the analysis cut-off date of 13 September 2013; median time on study drug was 167 days in the tivozanib group and 162 days in the bevacizumab group

End point values	Tivozanib + mFOLFOX6	Bevacizumab + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	88		
Units: months				
median (confidence interval 95%)	9.4 (8.5 to 10.1)	10.7 (7.5 to 12.8)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

An interim futility analysis was planned to be performed when approximately 83 investigator-assessed PFS events (50% of the total PFS events) were observed. The Lans DeMets beta spending function with an O'Brien-Fleming boundary was used to derive the futility boundary. If the HR for PFS was greater than 1.0581, enrollment was to be stopped. With this futility stopping rule, the adjusted study power was 78.6%.

Comparison groups	Tivozanib + mFOLFOX6 v Bevacizumab + mFOLFOX6
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Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.706 ^[1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.091
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.693
upper limit	1.718

Notes:

[1] - Stratification factors were LDH status (< 1.5 x ULN or ≥ 1.5 x ULN), origin of cancer (rectal or colon) and number of metastatic sites (1 or ≥ 2).

Secondary: Progression-Free Survival (PFS) based on Independent Radiological Review (IRR)

End point title	Progression-Free Survival (PFS) based on Independent Radiological Review (IRR)
End point description:	The time from the date of randomization until the date of radiological disease progression assessed by the IRR or until death due to any cause, even in the absence of radiological progression.
End point type	Secondary
End point timeframe:	3 Years

End point values	Tivozanib + mFOLFOX6	Bevacizumab + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[2]	0 ^[3]		
Units: months				

Notes:

[2] - Due to the early termination of the study, this endpoint was was not assessed.

[3] - Due to the early termination of the study, this endpoint was was not assessed.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)
End point description:	The time from the date of randomization until the documented date of death. Participants still alive at the time of analysis were censored on the last day the participant was known to be alive.
Overall Survival in months could not be estimated due to low number of events at the time of interim analysis, instead the number of participants who died is presented.	
The analysis population is the FAS.	
End point type	Secondary

End point timeframe:

From randomization until the analysis cut-off date of 13 September 2013; median time on study drug was 167 days in the tivozanib group and 162 days in the bevacizumab group

End point values	Tivozanib + mFOLFOX6	Bevacizumab + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	88		
Units: participants	26	12		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Tivozanib + mFOLFOX6 v Bevacizumab + mFOLFOX6
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.754 ^[4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.116
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.561
upper limit	2.218

Notes:

[4] - Stratification factors were LDH status ($< 1.5 \times \text{ULN}$ or $\geq 1.5 \times \text{ULN}$), origin of cancer (rectal or colon) and number of metastatic sites (1 or ≥ 2).

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)
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End point description:

The percentage of participants with a best overall response of complete response (CR) or partial response (PR) confirmed a minimum of four weeks apart based on RECIST 1.1 criteria.

CR: Disappearance of all target and non-target lesions and no new lesions.

PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters and no progression of non-target lesions and no new lesions, or, disappearance of all target lesions and persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits and no new lesions.

The analysis population is the FAS.

End point type	Secondary
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End point timeframe:

From randomization until the analysis cut-off date of 13 September 2013; median time on study drug was 167 days in the tivozanib group and 162 days in the bevacizumab group

End point values	Tivozanib + mFOLFOX6	Bevacizumab + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	88		
Units: percentage of participants				
number (not applicable)	45.2	43.2		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Tivozanib + mFOLFOX6 v Bevacizumab + mFOLFOX6
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.718 ^[5]
Method	Cochran-Mantel-Haenszel

Notes:

[5] - Stratification factors were LDH status ($< 1.5 \times \text{ULN}$ or $\geq 1.5 \times \text{ULN}$), origin of cancer (rectal or colon) and number of metastatic sites (1 or ≥ 2).

Secondary: Duration of Response (DoR)

End point title	Duration of Response (DoR)
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End point description:

The time from the date of the first documented response of CR or PR (whichever is first recorded) to documented progression or death. If a participant did not progress or had not died at the time of analysis, the duration of response was censored at the date of last tumor assessment. Duration of response is only defined for participants whose best overall response was CR or PR.

The analysis population is the FAS.

End point type	Secondary
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End point timeframe:

From randomization until the analysis cut-off date of 13 September 2013; median time on study drug was 167 days in the tivozanib group and 162 days in the bevacizumab group

End point values	Tivozanib + mFOLFOX6	Bevacizumab + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	38		
Units: months				
median (confidence interval 95%)	7.4 (5.6 to 11.3)	9.3 (7.3 to 10.7)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Tivozanib + mFOLFOX6 v Bevacizumab + mFOLFOX6
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.437 ^[6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.389
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.604
upper limit	3.194

Notes:

[6] - Stratification factors were LDH status (< 1.5 x ULN or ≥ 1.5 x ULN), origin of cancer (rectal or colon) and number of metastatic sites (1 or ≥ 2).

Secondary: Time to Treatment Failure (TTF)

End point title	Time to Treatment Failure (TTF)
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End point description:

The time from randomization to last dose date of tivozanib/bevacizumab. If a participant discontinued treatment for any reason, the participant was considered as an event. Participants remaining on treatment at the time of analysis were censored at date of last dose.

The analysis population is the FAS.

End point type	Secondary
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End point timeframe:

From randomization until the analysis cut-off date of 13 September 2013; median time on study drug was 167 days in the tivozanib group and 162 days in the bevacizumab group

End point values	Tivozanib + mFOLFOX6	Bevacizumab + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	88		
Units: months				
median (confidence interval 95%)	5.5 (4.9 to 7.1)	5.4 (3.7 to 6.7)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Tivozanib + mFOLFOX6 v Bevacizumab + mFOLFOX6

Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.967 ^[7]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.006
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.746
upper limit	1.358

Notes:

[7] - Stratification factors were LDH status ($< 1.5 \times \text{ULN}$ or $\geq 1.5 \times \text{ULN}$), origin of cancer (rectal or colon) and number of metastatic sites (1 or ≥ 2).

Secondary: Health Related Quality of life (HRQoL)

End point title	Health Related Quality of life (HRQoL)
End point description:	Defined as the time to deterioration in HRQoL measured by the CRC subscale of the FACT-C scale, change in score from baseline using the EQ-5D and FCSI (FACT Colorectal Symptom Index).
End point type	Secondary
End point timeframe:	3 Years

End point values	Tivozanib + mFOLFOX6	Bevacizumab + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[8]	0 ^[9]		
Units: scores in a scale				

Notes:

[8] - Due to the early termination of the study, this endpoint was not assessed.

[9] - Due to the early termination of the study, this endpoint was not assessed.

Statistical analyses

No statistical analyses for this end point

Secondary: Safety as assessed by Physical Examination, Vital Signs, Laboratory Assessments, 12-lead Electrocardiogram (ECGs), and Adverse Events

End point title	Safety as assessed by Physical Examination, Vital Signs, Laboratory Assessments, 12-lead Electrocardiogram (ECGs), and Adverse Events
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End point description:

An adverse event (AE) was defined as any untoward medical occurrence in a patient administered a study drug or who had undergone study procedures and did not necessarily have a causal relationship with this treatment. An AE could therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a study drug, whether or not related to the study drug. An AE was considered "serious" (SAE) if it resulted in death; was life threatening; resulted in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions; resulted in a congenital anomaly or birth defect; required inpatient hospitalization or led to prolongation of hospitalization. AEs, including abnormal clinical laboratory values, were to be graded using the National Cancer Institute Common Terminology Criteria

for Grading Adverse Events (NCI-CTCAE) guidelines (v4.03).

End point type	Secondary
End point timeframe:	
From the first dose through 30 days after last dose of either tivozanib or bevacizumab, until the data cut-off date of 28 February 2014; median time of treatment was 168 days in the tivozanib arm and 162 days in the bevacizumab arm	

End point values	Tivozanib + mFOLFOX6	Bevacizumab + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	87		
Units: participants				
Any AE	177	87		
CTCAE Grade ≥ 3 AE	156	76		
Any tivozanib (tivo)/bevacizumab (beva)-related AE	158	74		
Any mFOLFOX6-related AE	169	84		
Any tivo/beva and mFOLFOX6-related AE	138	59		
Any tivo/beva-related AE CTCAE Grade ≥ 3	104	31		
Any mFOLFOX6-related AE with CTCAE Grade ≥ 3	126	61		
Any tivo/beva & mFOLFOX6-related CTCAE Grade ≥ 3	75	23		
Any AE with an outcome of death	8	2		
Any tivo/beva-related AE w/ an outcome of death	3	2		
Any mFOLFOX6-related AE w/ an outcome of death	3	2		
Any tivo/beva & mFOLFOX6-related AE of death	3	2		
Any serious AE	82	42		
Any tivo/beva-related SAE	38	15		
Any mFOLFOX6-related SAE	45	23		
Any tivo/beva & mFOLFOX6-related SAE	30	11		
Any AE leading to tivo/beva discontinuation	73	30		
Any AE leading to tivo/beva interruption	138	63		
Any AE leading to tivo/beva reduction	17	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival Events by Lactate Dehydrogenase (LDH) Level

End point title	Progression-free Survival Events by Lactate Dehydrogenase (LDH) Level
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End point description:

The number of participants with a progression-free survival event (radiological progression assessed by the investigator or death due to any cause) reported by Baseline serum lactate dehydrogenase status.

End point type	Secondary
End point timeframe:	
From randomization until the analysis cut-off date of 13 September 2013; median time on study drug was 167 days in the tivozanib group and 162 days in the bevacizumab group	

End point values	Tivozanib + mFOLFOX6: LDH < 1.5 ULN	Bevacizumab + mFOLFOX6: LDH < 1.5 ULN	Tivozanib + mFOLFOX6: LDH ≥ 1.5 ULN	Bevacizumab + mFOLFOX6: LDH ≥ 1.5 ULN
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	127	64	50	24
Units: participants	42	16	24	13

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Tivozanib + mFOLFOX6: LDH < 1.5 ULN v Bevacizumab + mFOLFOX6: LDH < 1.5 ULN
Number of subjects included in analysis	191
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	1.331
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.746
upper limit	2.375

Statistical analysis title	Statistical Analysis 2
Comparison groups	Tivozanib + mFOLFOX6: LDH ≥ 1.5 ULN v Bevacizumab + mFOLFOX6: LDH ≥ 1.5 ULN
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.575
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.285
upper limit	1.16

Secondary: Progression-free Survival Events by Serum Vascular Endothelial Growth

Factor-A (VEGF-A) Level

End point title	Progression-free Survival Events by Serum Vascular Endothelial Growth Factor-A (VEGF-A) Level
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End point description:

The number of participants with a progression-free survival event (radiological progression assessed by the investigator or death due to any cause) reported by Baseline serum vascular endothelial growth factor-A (VEGF-A) level. VEGF-A protein levels were quantified using enzyme-linked immunosorbent assay (ELISA); the level of protein is expressed relative to the observed median level.

End point type	Secondary
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End point timeframe:

From randomization until the analysis cut-off date of 13 September 2013; median time on study drug was 167 days in the tivozanib group and 162 days in the bevacizumab group

End point values	Tivozanib + mFOLFOX6: VEGF-A < Median	Bevacizumab + mFOLFOX6: VEGF-A < Median	Tivozanib + mFOLFOX6: VEGF-A ≥ Median	Bevacizumab + mFOLFOX6: VEGF-A ≥ Median
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	54	29	54	26
Units: participants	20	6	24	12

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Tivozanib + mFOLFOX6: VEGF-A < Median v Bevacizumab + mFOLFOX6: VEGF-A < Median
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	1.608
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.635
upper limit	4.073

Statistical analysis title	Statistical Analysis 2
Comparison groups	Tivozanib + mFOLFOX6: VEGF-A ≥ Median v Bevacizumab + mFOLFOX6: VEGF-A ≥ Median
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.755

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.375
upper limit	1.521

Secondary: Progression-free Survival Events by Serum Vascular Endothelial Growth Factor-C (VEGF-C) Level

End point title	Progression-free Survival Events by Serum Vascular Endothelial Growth Factor-C (VEGF-C) Level
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End point description:

The number of participants with a progression-free survival event (radiological progression assessed by the investigator or death due to any cause) reported by Baseline serum VEGF-C level. VEGF-C protein levels were quantified using enzyme-linked immunosorbent assay (ELISA); the level of protein is expressed relative to the observed median level.

End point type	Secondary
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End point timeframe:

From randomization until the analysis cut-off date of 13 September 2013; median time on study drug was 167 days in the tivozanib group and 162 days in the bevacizumab group

End point values	Tivozanib + mFOLFOX6: VEGF-C < Median	Bevacizumab + mFOLFOX6: VEGF-C < Median	Tivozanib + mFOLFOX6: VEGF-C ≥ Median	Bevacizumab + mFOLFOX6: VEGF-C ≥ Median
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	52	27	56	28
Units: participants	15	8	29	10

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Bevacizumab + mFOLFOX6: VEGF-C < Median v Tivozanib + mFOLFOX6: VEGF-C < Median
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.877
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.366
upper limit	2.1

Statistical analysis title	Statistical Analysis 2
Comparison groups	Tivozanib + mFOLFOX6: VEGF-C \geq Median v Bevacizumab + mFOLFOX6: VEGF-C \geq Median
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	1.275
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.614
upper limit	2.646

Secondary: Progression-free Survival Events by Serum VEGF-C/VEGF-A Ratio

End point title	Progression-free Survival Events by Serum VEGF-C/VEGF-A Ratio
End point description:	The number of participants with a progression-free survival event (radiological progression assessed by the investigator or death due to any cause) reported by Baseline serum VEGF-C/VEGF-A ratio. VEGF-A and VEGF-C protein levels were quantified using enzyme-linked immunosorbent assay (ELISA); the ratio is expressed relative to the observed median level.
End point type	Secondary
End point timeframe:	From randomization until the analysis cut-off date of 13 September 2013; median time on study drug was 167 days in the tivozanib group and 162 days in the bevacizumab group

End point values	Tivozanib + mFOLFOX6: VEGF-C/VEGF-A < Median	Bevacizumab + mFOLFOX6: VEGF-C/VEGF-A < Median	Tivozanib + mFOLFOX6: VEGF-C/VEGF-A \geq Median	Bevacizumab + mFOLFOX6: VEGF-C/VEGF-A \geq Median
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	53	26	55	29
Units: participants	21	11	23	7

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Tivozanib + mFOLFOX6: VEGF-C/VEGF-A < Median v Bevacizumab + mFOLFOX6: VEGF-C/VEGF-A < Median
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.721

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.345
upper limit	1.507

Statistical analysis title	Statistical Analysis 2
Comparison groups	Tivozanib + mFOLFOX6: VEGF-C/VEGF-A \geq Median v Bevacizumab + mFOLFOX6: VEGF-C/VEGF-A \geq Median
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	1.597
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.672
upper limit	3.795

Secondary: Progression-Free Survival Events by Soluble Vascular Endothelial Growth Factor Receptor-2 (sVEGFR-2) Level

End point title	Progression-Free Survival Events by Soluble Vascular Endothelial Growth Factor Receptor-2 (sVEGFR-2) Level
End point description:	
The number of participants with a progression-free survival event (radiological progression assessed by the investigator or death due to any cause) reported by Baseline serum sVEGFR-2 level. sVEGFR-2 protein levels were quantified using enzyme-linked immunosorbent assay (ELISA); the level of protein is expressed relative to the observed median level.	
End point type	Secondary
End point timeframe:	
From randomization until the analysis cut-off date of 13 September 2013; median time on study drug was 167 days in the tivozanib group and 162 days in the bevacizumab group	

End point values	Tivozanib + mFOLFOX6: sVEGFR-2 < Median	Bevacizumab + mFOLFOX6: sVEGFR-2 < Median	Tivozanib + mFOLFOX6: sVEGFR-2 \geq Median	Bevacizumab + mFOLFOX6: sVEGFR-2 \geq Median
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	46	27	62	28
Units: participants	15	5	29	13

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Tivozanib + mFOLFOX6: sVEGFR-2 < Median v Bevacizumab + mFOLFOX6: sVEGFR-2 < Median
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	1.627
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	4.564

Statistical analysis title	Statistical Analysis 2
Comparison groups	Tivozanib + mFOLFOX6: sVEGFR-2 ≥ Median v Bevacizumab + mFOLFOX6: sVEGFR-2 ≥ Median
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.779
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.397
upper limit	1.531

Secondary: Progression-Free Survival Events by Soluble Vascular Endothelial Growth Factor Receptor-3 (sVEGFR-3) Level

End point title	Progression-Free Survival Events by Soluble Vascular Endothelial Growth Factor Receptor-3 (sVEGFR-3) Level
End point description: The number of participants with a progression-free survival event (radiological progression assessed by the investigator or death due to any cause) reported by Baseline serum sVEGFR-3 level. sVEGFR-3 protein levels were quantified using enzyme-linked immunosorbent assay (ELISA); the level of protein is expressed relative to the observed median level.	
End point type	Secondary
End point timeframe: From randomization until the analysis cut-off date of 13 September 2013; median time on study drug was 167 days in the tivozanib group and 162 days in the bevacizumab group	

End point values	Tivozanib + mFOLFOX6: sVEGFR-3 < Median	Bevacizumab + mFOLFOX6: sVEGFR-3 < Median	Tivozanib + mFOLFOX6: sVEGFR-3 ≥ Median	Bevacizumab + mFOLFOX6: sVEGFR-3 ≥ Median
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	50	30	58	25
Units: participants	14	4	30	14

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Tivozanib + mFOLFOX6: sVEGFR-3 < Median v Bevacizumab + mFOLFOX6: sVEGFR-3 < Median
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	1.946
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.636
upper limit	5.956

Statistical analysis title	Statistical Analysis 2
Comparison groups	Tivozanib + mFOLFOX6: sVEGFR-3 ≥ Median v Bevacizumab + mFOLFOX6: sVEGFR-3 ≥ Median
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.806
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.422
upper limit	1.538

Secondary: Progression-Free Survival Events by Serum Interleukin-8 (IL-8) Level

End point title	Progression-Free Survival Events by Serum Interleukin-8 (IL-8) Level
End point description:	
The number of participants with a progression-free survival event (radiological progression assessed by the investigator or death due to any cause) reported by Baseline serum interleukin-8 level. IL-8 protein levels were quantified using enzyme-linked immunosorbent assay (ELISA); the level of protein is expressed relative to the observed median level.	
End point type	Secondary

End point timeframe:

From randomization until the analysis cut-off date of 13 September 2013; median time on study drug was 167 days in the tivozanib group and 162 days in the bevacizumab group

End point values	Tivozanib + mFOLFOX6: IL-8 < Median	Bevacizumab + mFOLFOX6: IL-8 < Median	Tivozanib + mFOLFOX6: IL-8 ≥ Median	Bevacizumab + mFOLFOX6: IL-8 ≥ Median
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	53	27	55	28
Units: participants	14	7	30	11

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Tivozanib + mFOLFOX6: IL-8 < Median v Bevacizumab + mFOLFOX6: IL-8 < Median
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.776
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.303
upper limit	1.991

Statistical analysis title	Statistical Analysis 2
Comparison groups	Tivozanib + mFOLFOX6: IL-8 ≥ Median v Bevacizumab + mFOLFOX6: IL-8 ≥ Median
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	1.241
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.615
upper limit	2.501

Secondary: Progression-Free Survival Events by Serum Neuropilin Level

End point title	Progression-Free Survival Events by Serum Neuropilin Level
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End point description:

The number of participants with a progression-free survival event (radiological progression assessed by the investigator or death due to any cause) reported by Baseline serum neuropilin level. Neuropilin protein levels were quantified using enzyme-linked immunosorbent assay (ELISA); the level of protein is expressed relative to the observed median level.

End point type	Secondary
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End point timeframe:

From randomization until the analysis cut-off date of 13 September 2013; median time on study drug was 167 days in the tivozanib group and 162 days in the bevacizumab group

End point values	Tivozanib + mFOLFOX6: Neuropilin < Median	Bevacizumab + mFOLFOX6: Neuropilin < Median	Tivozanib + MFOLFOX6: Neuropilin ≥ Median	Bevacizumab + mFOLFOX6: Neuropilin ≥ Median
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	53	30	55	25
Units: participants	10	6	34	12

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Tivozanib + mFOLFOX6: Neuropilin < Median v Bevacizumab + mFOLFOX6: Neuropilin < Median
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.343
upper limit	2.63

Statistical analysis title	Statistical Analysis 2
Comparison groups	Tivozanib + MFOLFOX6: Neuropilin ≥ Median v Bevacizumab + mFOLFOX6: Neuropilin ≥ Median
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.983
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.503
upper limit	1.918

Secondary: Progression-Free Survival Events by Tumor VEGF-A Ribonucleic Acid (RNA) Level

End point title	Progression-Free Survival Events by Tumor VEGF-A Ribonucleic Acid (RNA) Level
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End point description:

The number of participants with a progression-free survival event (radiological progression assessed by the investigator or death due to any cause) reported by Baseline tumor VEGF-A RNA level.

RNA was purified from biopsy tissue and measured using quantitative reverse transcription polymerase chain reaction (qRT-PCR). Since low cycle threshold (CT) values reflect high RNA expression, the inverse of CT values were used to derive tumor categories. RNA level is expressed relative to the observed median level.

End point type	Secondary
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End point timeframe:

From randomization until the analysis cut-off date of 13 September 2013; median time on study drug was 167 days in the tivozanib group and 162 days in the bevacizumab group

End point values	Tivozanib + mFOLFOX6: VEGF-A RNA < Median	Bevacizumab + mFOLFOX6: VEGF-A RNA < Median	Tivozanib + mFOLFOX6: VEGF-A RNA ≥ Median	Bevacizumab + mFOLFOX6: VEGF-A RNA ≥ Median
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	18	38	17
Units: participants	13	7	18	5

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Tivozanib + mFOLFOX6: VEGF-A RNA < Median v Bevacizumab + mFOLFOX6: VEGF-A RNA < Median
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	1.226
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.468
upper limit	3.214

Statistical analysis title	Statistical Analysis 2
Comparison groups	Tivozanib + mFOLFOX6: VEGF-A RNA ≥ Median v Bevacizumab + mFOLFOX6: VEGF-A RNA ≥ Median

Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	1.232
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.447
upper limit	3.396

Secondary: Progression-Free Survival Events by Tumor VEGF-C RNA Level

End point title	Progression-Free Survival Events by Tumor VEGF-C RNA Level
End point description:	
The number of participants with a progression-free survival event (radiological progression assessed by the investigator or death due to any cause) reported by Baseline tumor VEGF-C RNA level.	
RNA was purified from biopsy tissue and measured using quantitative reverse transcription polymerase chain reaction (qRT-PCR). Since low cycle threshold (CT) values reflect high RNA expression, the inverse of CT values were used to derive tumor categories. RNA level is expressed relative to the observed median level.	
End point type	Secondary
End point timeframe:	
From randomization until the analysis cut-off date of 13 September 2013; median time on study drug was 167 days in the tivozanib group and 162 days in the bevacizumab group	

End point values	Tivozanib + mFOLFOX6: VEGF-C RNA < Median	Bevacizumab + mFOLFOX6: VEGF-C RNA < Median	Tivozanib + mFOLFOX6: VEGF-C RNA ≥ Median	Bevacizumab + mFOLFOX6: VEGF-C RNA ≥ Median
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	41	16	37	19
Units: participants	14	6	17	6

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Tivozanib + mFOLFOX6: VEGF-C RNA < Median v Bevacizumab + mFOLFOX6: VEGF-C RNA < Median
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.803

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.307
upper limit	2.1

Statistical analysis title	Statistical Analysis 2
Comparison groups	Tivozanib + mFOLFOX6: VEGF-C RNA \geq Median v Bevacizumab + mFOLFOX: VEGF-C RNA \geq Median
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	1.505
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.585
upper limit	3.873

Secondary: Progression-Free Survival Events by Tumor VEGF-C/VEGF-A RNA Ratio

End point title	Progression-Free Survival Events by Tumor VEGF-C/VEGF-A RNA Ratio
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End point description:

The number of participants with a progression-free survival event (radiological progression assessed by the investigator or death due to any cause) reported by Baseline tumor VEGF-C/VEGF-A RNA ratio.

RNA was purified from biopsy tissue and measured using quantitative reverse transcription polymerase chain reaction (qRT-PCR). Since low cycle threshold (CT) values reflect high RNA expression, the inverse of CT values were used to derive tumor categories. RNA level is expressed relative to the observed median level.

End point type	Secondary
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End point timeframe:

From randomization until the analysis cut-off date of 13 September 2013; median time on study drug was 167 days in the tivozanib group and 162 days in the bevacizumab group

End point values	Tivozanib + mFOLFOX6: VEGF-C/VEGF-A RNA < Median	Bevacizumab + mFOLFOX6: VEGF-C/VEGF-A RNA < Median	Tivozanib + mFOLFOX6: VEGF-C/VEGF-A RNA \geq Median	Bevacizumab + mFOLFOX6: VEGF-C/VEGF-A RNA \geq Median
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	38	16	40	19
Units: participants	16	6	15	6

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Tivozanib + mFOLFOX6: VEGF-C/VEGF-A RNA < Median v Bevacizumab + mFOLFOX6: VEGF-C/VEGF-A RNA < Median
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.921
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.356
upper limit	2.385

Statistical analysis title	Statistical Analysis 2
Comparison groups	Tivozanib + mFOLFOX6: VEGF-C/VEGF-A RNA \geq Median v Bevacizumab + mFOLFOX6: VEGF-C/VEGF-A RNA \geq Median
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.462
upper limit	3.22

Secondary: Progression-Free Survival Events by Tumor VEGF-D RNA Level

End point title	Progression-Free Survival Events by Tumor VEGF-D RNA Level
End point description:	
The number of participants with a progression-free survival event (radiological progression assessed by the investigator or death due to any cause) reported by Baseline tumor VEGF-D RNA level.	
RNA was purified from biopsy tissue and measured using quantitative reverse transcription polymerase chain reaction (qRT-PCR). Since low cycle threshold (CT) values reflect high RNA expression, the inverse of CT values were used to derive tumor categories. RNA level is expressed relative to the observed median level.	
End point type	Secondary
End point timeframe:	
From randomization until the analysis cut-off date of 13 September 2013; median time on study drug was 167 days in the tivozanib group and 162 days in the bevacizumab group	

End point values	Tivozanib + mFOLFOX6: VEGF-D RNA < Median	Bevacizumab + mFOLFOX6: VEGF-D RNA < Median	Tivozanib + mFOLFOX6: VEGF-D RNA ≥ Median	Bevacizumab + mFOLFOX6: VEGF-D RNA ≥ Median
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	42	14	36	21
Units: participants	16	5	15	7

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Tivozanib + mFOLFOX6: VEGF-D RNA < Median v Bevacizumab + mFOLFOX6: VEGF-D RNA < Median
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.915
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.334
upper limit	2.512

Statistical analysis title	Statistical Analysis 2
Comparison groups	Tivozanib + mFOLFOX6: VEGF-D RNA ≥ Median v Bevacizumab + mFOLFOX6: VEGF-D RNA ≥ Median
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	1.384
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.554
upper limit	3.455

Secondary: Progression-Free Survival Events by Tumor Placental Growth Factor (PIGF) RNA Level

End point title	Progression-Free Survival Events by Tumor Placental Growth Factor (PIGF) RNA Level
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End point description:

The number of participants with a progression-free survival event (radiological progression assessed by the investigator or death due to any cause) reported by Baseline tumor PIGF RNA level.

RNA was purified from biopsy tissue and measured using quantitative reverse transcription polymerase

chain reaction (qRT-PCR). Since low cycle threshold (CT) values reflect high RNA expression, the inverse of CT values were used to derive tumor categories. RNA level is expressed relative to the observed median level.

End point type	Secondary
End point timeframe:	
From randomization until the analysis cut-off date of 13 September 2013; median time on study drug was 167 days in the tivozanib group and 162 days in the bevacizumab group	

End point values	Tivozanib + mFOLFOX6: PIGF RNA < Median	Bevacizumab + mFOLFOX6: PIGF RNA < Median	Tivozanib + mFOLFOX6: PIGF RNA ≥ Median	Bevacizumab + mFOLFOX6: PIGF RNA ≥ Median
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	39	17	39	18
Units: participants	14	5	17	7

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Tivozanib + mFOLFOX6: PIGF RNA < Median v Bevacizumab + mFOLFOX6: PIGF RNA < Median
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	1.538
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.548
upper limit	4.32

Statistical analysis title	Statistical Analysis 2
Comparison groups	Tivozanib + mFOLFOX6: PIGF RNA ≥ Median v Bevacizumab + mFOLFOX6: PIGF RNA ≥ Median
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.744
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.299
upper limit	1.85

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first study drug intake (tivozanib/bevacizumab) until 30 days after the last study drug intake, until the data cut-off date of 28 Feb 2014. The median duration of treatment was 168 days in the tivozanib arm and 162 days in the bevacizumab arm

Adverse event reporting additional description:

The Safety Analysis Set (SAF) includes all patients who received 1 dose of drug.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	13.1
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Reporting groups

Reporting group title	Tivozanib + mFOLFOX6
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Reporting group description:

Participants received 1.5 mg of tivozanib orally once daily beginning on Day 1 of each cycle for 21 days followed by 7 days off treatment. Participants also received mFOLFOX6 chemotherapy every 2 weeks on Days 1 and 15 of each cycle.

Reporting group title	Bevacizumab + mFOLFOX6
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Reporting group description:

Participants received a dose of 5 mg/kg bevacizumab via intravenous infusion every 2 weeks on Days 1 and 15 of each cycle. Participants also received mFOLFOX6 chemotherapy every 2 weeks on Days 1 and 15 of each cycle.

Serious adverse events	Tivozanib + mFOLFOX6	Bevacizumab + mFOLFOX6	
Total subjects affected by serious adverse events			
subjects affected / exposed	82 / 177 (46.33%)	42 / 87 (48.28%)	
number of deaths (all causes)	8	2	
number of deaths resulting from adverse events	3	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Angiomyolipoma			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal neoplasm			

subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	3 / 177 (1.69%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	2 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 177 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	4 / 177 (2.26%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive emergency			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	0 / 177 (0.00%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein thrombosis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			

subjects affected / exposed	2 / 177 (1.13%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Anorectal operation			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chemotherapy			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 177 (1.13%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Catheter site erythema			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 177 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Disease progression			
subjects affected / exposed	3 / 177 (1.69%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Fatigue			
subjects affected / exposed	2 / 177 (1.13%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 177 (0.56%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised oedema			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 177 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	0 / 177 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	4 / 177 (2.26%)	7 / 87 (8.05%)	
occurrences causally related to treatment / all	3 / 5	2 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stent malfunction			

subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 177 (0.56%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Vaginal fistula			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 177 (1.69%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			

subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	7 / 177 (3.95%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	5 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 177 (0.56%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 177 (0.56%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart rate increased			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin increased			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural			

complications			
Alcohol poisoning			
subjects affected / exposed	0 / 177 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	0 / 177 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound necrosis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Aortic valve disease			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 177 (0.56%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	2 / 177 (1.13%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiopulmonary failure			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intracardiac thrombus			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 177 (0.56%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 177 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Headache			

subjects affected / exposed	1 / 177 (0.56%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoparesis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reversible posterior leukoencephalopathy syndrome			
subjects affected / exposed	2 / 177 (1.13%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 177 (0.56%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	2 / 177 (1.13%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	2 / 177 (1.13%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			

subjects affected / exposed	5 / 177 (2.82%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	2 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	3 / 177 (1.69%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic thrombocytopenic purpura			
subjects affected / exposed	0 / 177 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 177 (0.56%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	5 / 177 (2.82%)	4 / 87 (4.60%)	
occurrences causally related to treatment / all	1 / 6	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal ulcer			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			

subjects affected / exposed	2 / 177 (1.13%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic obstruction			
subjects affected / exposed	1 / 177 (0.56%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 177 (0.56%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	7 / 177 (3.95%)	5 / 87 (5.75%)	
occurrences causally related to treatment / all	3 / 7	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			

subjects affected / exposed	1 / 177 (0.56%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal obstruction			
subjects affected / exposed	4 / 177 (2.26%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	1 / 5	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 177 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	1 / 177 (0.56%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 177 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Nausea			
subjects affected / exposed	3 / 177 (1.69%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumatosis intestinalis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			

subjects affected / exposed	1 / 177 (0.56%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	2 / 177 (1.13%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	5 / 177 (2.82%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	2 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic haemorrhage			
subjects affected / exposed	0 / 177 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Jaundice cholestatic			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (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	1 / 177 (0.56%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal failure acute			
subjects affected / exposed	0 / 177 (0.00%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	0 / 177 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc degeneration			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mobility decreased			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Arthritis bacterial			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bacteraemia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	2 / 177 (1.13%)	3 / 87 (3.45%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis viral			
subjects affected / exposed	0 / 177 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 177 (0.56%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 177 (0.56%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			

subjects affected / exposed	3 / 177 (1.69%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perihepatic abscess			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 177 (0.56%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	4 / 177 (2.26%)	4 / 87 (4.60%)	
occurrences causally related to treatment / all	2 / 4	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin infection			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			

subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	0 / 177 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 177 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			

subjects affected / exposed	1 / 177 (0.56%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 177 (0.56%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Tivozanib + mFOLFOX6	Bevacizumab + mFOLFOX6	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	176 / 177 (99.44%)	87 / 87 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	77 / 177 (43.50%)	25 / 87 (28.74%)	
occurrences (all)	137	39	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	37 / 177 (20.90%)	17 / 87 (19.54%)	
occurrences (all)	77	27	
Chest pain			
subjects affected / exposed	2 / 177 (1.13%)	5 / 87 (5.75%)	
occurrences (all)	2	6	
Fatigue			
subjects affected / exposed	95 / 177 (53.67%)	45 / 87 (51.72%)	
occurrences (all)	221	90	
Infusion related reaction			
subjects affected / exposed	9 / 177 (5.08%)	3 / 87 (3.45%)	
occurrences (all)	15	3	
Mucosal inflammation			
subjects affected / exposed	40 / 177 (22.60%)	28 / 87 (32.18%)	
occurrences (all)	85	50	
Oedema peripheral			

subjects affected / exposed occurrences (all)	14 / 177 (7.91%) 15	6 / 87 (6.90%) 9	
Pain subjects affected / exposed occurrences (all)	5 / 177 (2.82%) 6	5 / 87 (5.75%) 5	
Pyrexia subjects affected / exposed occurrences (all)	17 / 177 (9.60%) 24	13 / 87 (14.94%) 16	
Temperature intolerance subjects affected / exposed occurrences (all)	11 / 177 (6.21%) 16	9 / 87 (10.34%) 10	
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	3 / 177 (1.69%) 3	6 / 87 (6.90%) 9	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	20 / 177 (11.30%) 25	12 / 87 (13.79%) 16	
Dysphonia subjects affected / exposed occurrences (all)	42 / 177 (23.73%) 59	13 / 87 (14.94%) 14	
Dyspnoea subjects affected / exposed occurrences (all)	26 / 177 (14.69%) 28	13 / 87 (14.94%) 15	
Epistaxis subjects affected / exposed occurrences (all)	33 / 177 (18.64%) 45	25 / 87 (28.74%) 30	
Hiccups subjects affected / exposed occurrences (all)	10 / 177 (5.65%) 20	2 / 87 (2.30%) 5	
Oropharyngeal pain subjects affected / exposed occurrences (all)	16 / 177 (9.04%) 18	6 / 87 (6.90%) 7	
Psychiatric disorders			

Anxiety subjects affected / exposed occurrences (all)	8 / 177 (4.52%) 9	6 / 87 (6.90%) 9	
Insomnia subjects affected / exposed occurrences (all)	23 / 177 (12.99%) 38	15 / 87 (17.24%) 41	
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	10 / 177 (5.65%) 16	3 / 87 (3.45%) 3	
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	10 / 177 (5.65%) 14	4 / 87 (4.60%) 4	
Blood thyroid stimulating hormone increased subjects affected / exposed occurrences (all)	9 / 177 (5.08%) 10	0 / 87 (0.00%) 0	
Neutrophil count decreased subjects affected / exposed occurrences (all)	14 / 177 (7.91%) 23	8 / 87 (9.20%) 17	
Platelet count decreased subjects affected / exposed occurrences (all)	10 / 177 (5.65%) 16	3 / 87 (3.45%) 7	
Weight decreased subjects affected / exposed occurrences (all)	34 / 177 (19.21%) 45	7 / 87 (8.05%) 7	
Nervous system disorders			
Amnesia subjects affected / exposed occurrences (all)	1 / 177 (0.56%) 1	5 / 87 (5.75%) 5	
Dizziness subjects affected / exposed occurrences (all)	17 / 177 (9.60%) 17	6 / 87 (6.90%) 6	
Dysaesthesia subjects affected / exposed occurrences (all)	12 / 177 (6.78%) 39	5 / 87 (5.75%) 12	
Dysgeusia			

subjects affected / exposed	26 / 177 (14.69%)	18 / 87 (20.69%)	
occurrences (all)	33	21	
Headache			
subjects affected / exposed	28 / 177 (15.82%)	12 / 87 (13.79%)	
occurrences (all)	42	14	
Hypoaesthesia			
subjects affected / exposed	5 / 177 (2.82%)	5 / 87 (5.75%)	
occurrences (all)	10	7	
Lethargy			
subjects affected / exposed	11 / 177 (6.21%)	3 / 87 (3.45%)	
occurrences (all)	30	17	
Neuropathy peripheral			
subjects affected / exposed	74 / 177 (41.81%)	34 / 87 (39.08%)	
occurrences (all)	181	87	
Neurotoxicity			
subjects affected / exposed	10 / 177 (5.65%)	3 / 87 (3.45%)	
occurrences (all)	21	4	
Paraesthesia			
subjects affected / exposed	46 / 177 (25.99%)	20 / 87 (22.99%)	
occurrences (all)	108	40	
Peripheral sensory neuropathy			
subjects affected / exposed	21 / 177 (11.86%)	13 / 87 (14.94%)	
occurrences (all)	45	24	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	20 / 177 (11.30%)	9 / 87 (10.34%)	
occurrences (all)	30	24	
Leukopenia			
subjects affected / exposed	19 / 177 (10.73%)	9 / 87 (10.34%)	
occurrences (all)	37	18	
Neutropenia			
subjects affected / exposed	93 / 177 (52.54%)	36 / 87 (41.38%)	
occurrences (all)	254	77	
Thrombocytopenia			
subjects affected / exposed	54 / 177 (30.51%)	13 / 87 (14.94%)	
occurrences (all)	256	33	

Eye disorders			
Conjunctivitis			
subjects affected / exposed	3 / 177 (1.69%)	5 / 87 (5.75%)	
occurrences (all)	3	5	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	42 / 177 (23.73%)	16 / 87 (18.39%)	
occurrences (all)	52	25	
Abdominal pain upper			
subjects affected / exposed	13 / 177 (7.34%)	8 / 87 (9.20%)	
occurrences (all)	28	9	
Aphthous stomatitis			
subjects affected / exposed	9 / 177 (5.08%)	1 / 87 (1.15%)	
occurrences (all)	22	2	
Constipation			
subjects affected / exposed	50 / 177 (28.25%)	32 / 87 (36.78%)	
occurrences (all)	87	49	
Diarrhoea			
subjects affected / exposed	101 / 177 (57.06%)	49 / 87 (56.32%)	
occurrences (all)	316	101	
Dry mouth			
subjects affected / exposed	9 / 177 (5.08%)	2 / 87 (2.30%)	
occurrences (all)	10	2	
Dyspepsia			
subjects affected / exposed	23 / 177 (12.99%)	9 / 87 (10.34%)	
occurrences (all)	37	14	
Dysphagia			
subjects affected / exposed	9 / 177 (5.08%)	3 / 87 (3.45%)	
occurrences (all)	9	3	
Flatulence			
subjects affected / exposed	6 / 177 (3.39%)	5 / 87 (5.75%)	
occurrences (all)	6	5	
Nausea			
subjects affected / exposed	97 / 177 (54.80%)	47 / 87 (54.02%)	
occurrences (all)	234	112	
Rectal haemorrhage			

subjects affected / exposed occurrences (all)	7 / 177 (3.95%) 7	5 / 87 (5.75%) 5	
Stomatitis subjects affected / exposed occurrences (all)	36 / 177 (20.34%) 51	14 / 87 (16.09%) 29	
Vomiting subjects affected / exposed occurrences (all)	59 / 177 (33.33%) 107	24 / 87 (27.59%) 37	
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	18 / 177 (10.17%) 19	14 / 87 (16.09%) 14	
Hyperhidrosis subjects affected / exposed occurrences (all)	1 / 177 (0.56%) 1	5 / 87 (5.75%) 6	
Palmar-plantar erythrodysesthesia syndrome subjects affected / exposed occurrences (all)	34 / 177 (19.21%) 58	7 / 87 (8.05%) 9	
Pruritus subjects affected / exposed occurrences (all)	7 / 177 (3.95%) 7	7 / 87 (8.05%) 8	
Rash subjects affected / exposed occurrences (all)	16 / 177 (9.04%) 29	4 / 87 (4.60%) 4	
Renal and urinary disorders			
Proteinuria subjects affected / exposed occurrences (all)	19 / 177 (10.73%) 60	5 / 87 (5.75%) 10	
Endocrine disorders			
Hypothyroidism subjects affected / exposed occurrences (all)	25 / 177 (14.12%) 28	1 / 87 (1.15%) 1	
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	10 / 177 (5.65%) 14	5 / 87 (5.75%) 24	

Back pain			
subjects affected / exposed	26 / 177 (14.69%)	12 / 87 (13.79%)	
occurrences (all)	36	16	
Muscle spasms			
subjects affected / exposed	3 / 177 (1.69%)	5 / 87 (5.75%)	
occurrences (all)	3	7	
Myalgia			
subjects affected / exposed	5 / 177 (2.82%)	5 / 87 (5.75%)	
occurrences (all)	8	6	
Neck pain			
subjects affected / exposed	2 / 177 (1.13%)	6 / 87 (6.90%)	
occurrences (all)	2	7	
Pain in extremity			
subjects affected / exposed	11 / 177 (6.21%)	6 / 87 (6.90%)	
occurrences (all)	19	7	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	8 / 177 (4.52%)	6 / 87 (6.90%)	
occurrences (all)	9	7	
Upper respiratory tract infection			
subjects affected / exposed	6 / 177 (3.39%)	5 / 87 (5.75%)	
occurrences (all)	6	5	
Urinary tract infection			
subjects affected / exposed	19 / 177 (10.73%)	11 / 87 (12.64%)	
occurrences (all)	26	17	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	63 / 177 (35.59%)	24 / 87 (27.59%)	
occurrences (all)	115	37	
Dehydration			
subjects affected / exposed	10 / 177 (5.65%)	7 / 87 (8.05%)	
occurrences (all)	13	10	
Hyperglycaemia			
subjects affected / exposed	8 / 177 (4.52%)	5 / 87 (5.75%)	
occurrences (all)	13	6	
Hypokalaemia			

subjects affected / exposed	20 / 177 (11.30%)	13 / 87 (14.94%)	
occurrences (all)	25	21	
Hypomagnesaemia			
subjects affected / exposed	12 / 177 (6.78%)	2 / 87 (2.30%)	
occurrences (all)	17	12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 September 2011	The interim analysis for futility was added to allow for the early stopping of the study if clinical benefit was not observed. An adjustment to the study power due to the addition of the interim analysis was noted.
01 November 2011	<p>The collection of a pharmacokinetic sample was added postdose on day 1 of cycle 1 and the postdose timing of pharmacokinetic sample collection was clarified to ensure pharmacokinetic samples were collected during the C_{max} period and during steady state.</p> <p>A postdose electrocardiogram (ECG) on day 1 of cycle 1 and a second ECG on day 15 of cycle 2 were added based on regulatory agency feedback.</p> <p>A section and an appendix were added describing the monitoring of common serious adverse events (SAEs) that could be anticipated to occur in the study population.</p> <p>Text was added to describe the recommended imaging modalities for the performance of the study CT and MRI scans.</p> <p>Life expectancy of ≥ 3 months was removed from the inclusion criteria as it is subsumed within the performance status and overall health status criteria.</p> <p>Language was added in the introduction noting that when tivozanib is administered with the mFOLFOX6 regimen, the expectedness determination should take into account the labeling of each specific marketed drug.</p>
07 February 2012	<p>The exclusion criterion for absolute neutrophil count (ANC) was revised from $< 1500/\text{mm}^3$ to $< 2000/\text{mm}^3$ based on regulatory agency feedback and to align with oxaliplatin product labeling.</p> <p>The exclusion criterion for the number of weeks required between major surgery and the first dose of study medication was reduced to align with bevacizumab product labeling.</p> <p>The description of the screening physical examination was revised to include a neurologic and dental examination, and a neurologic examination was specified as part of the directed physical examination on day 1 of each treatment cycle. The revisions were made based on regulatory agency feedback and to align with bevacizumab and oxaliplatin product labeling.</p> <p>The risks associated with treatment of bevacizumab and intravenous bisphosphonates were more clearly specified based regulatory agency feedback and to align with bevacizumab product labeling.</p> <p>In assessing central nervous system (CNS) symptoms in the context of dose reductions, text was added to clarify that a brain MRI should be performed to confirm the diagnosis if reversible posterior leukoencephalopathy syndrome (RPLS) was suspected. The revision was made based on regulatory agency feedback and to align with bevacizumab and oxaliplatin product labeling.</p> <p>Language was added to allow for randomization to occur up to 72 hours prior to the first dose of study drug due to logistics in obtaining components of the mFOLFOX6 chemotherapy backbone and/or bevacizumab.</p> <p>The criteria for starting the next cycle was revised with a lower platelet count to better reflect local practice and additional retreatment criteria relating to RPLS and proteinuria were added to align with bevacizumab and oxaliplatin product labeling.</p>

04 September 2012	<p>An analysis of PFS at 6 months comparing the 2 treatment arms was added due to toxicities associated with the mFOLFOX6 component of treatment with patients discontinuing the use of 1 or all components of the therapy after 6 months of use. The text relating to OS was revised to note patients could be contacted by site staff to collect long-term survival data to support key analyses.</p> <p>The decision criteria relating to the initiation of a phase 3 study was added to the sample size discussion for further transparency.</p> <p>The discontinuation criteria were revised to allow patients who became a candidate for surgical resection while on the study to resume study treatment after discussion with the Medical Monitor.</p> <p>The inclusion criteria for target lesions were clarified to note that for patients who had received prior radiotherapy, a target lesion could only be counted if it had progressed since the radiotherapy.</p> <p>The inclusion criteria for women and men of childbearing potential were updated to reduce the risk of pregnancy during the study.</p> <p>Language was added to clarify the actions needed for potential discontinuations from study treatment due to dose interruptions and to remind investigators of tivozanib's long half-life when determining subsequent therapy.</p> <p>Language was added to clarify other investigational drugs were prohibited during the study and to add agents that affect gastric pH to the list of prohibited concomitant medications as these agents may affect absorption of tivozanib.</p>
17 October 2012	<p>The appendix listing events that were to always be considered as serious events was removed as this related to an internal activity that the Sponsor would perform based on the events reported.</p> <p>The definition of postmenopausal and the use of effective birth control in sexually active patients were clarified.</p>
05 September 2013	<p>Language was added to provide clarification for continuing treatment with study treatment as randomized if enrollment was completed prior to the interim analysis for fertility.</p> <p>Necrotizing fasciitis was added to the criteria for the discontinuation of bevacizumab to align with updated bevacizumab product labeling.</p> <p>Language was added to provide clarification concerning the investigators' reporting obligations relating to events that the Sponsor classified as always serious.</p> <p>Given the potential for the censoring of patients for PFS events due to patients having discontinued treatment without radiographic evidence of progression, a modified definition of PFS was introduced for the determination of the timing of the final data analysis.</p> <p>The text for the analysis of TTF was corrected to indicate TTF was to be censored at the date of last dose of study drug.</p> <p>Language was added to clarify that a systematic process would be utilized for identifying and summarizing protocol deviations.</p> <p>A brief section was added to ensure the end of trial was clearly defined in accordance with relevant regulations and guidelines.</p>

03 March 2014	<p>The study was terminated due to the results of the interim futility analysis. As such, only those patients who continued to derive benefit from the treatment remained on study drug until 1 of the discontinuation criteria were met. Closure of the study was initiated on 21 Feb 2014 via a letter to the investigators and the protocol was updated to reflect the study termination. Patients who, in the opinion of the investigator and in consultation with the Sponsor's Medical Monitor, were continuing to derive benefit were allowed to continue to receive study treatment as randomized.</p> <p>The requirement for patients to follow the tumor assessment schedule if they discontinued treatment without radiological evidence of progression was removed. The requirement for patients to be followed for survival following the end-of-treatment visit was also removed.</p> <p>Termination language was added to clarify that only those patients who continued to derive benefit from the treatment were to remain on study.</p> <p>The discontinuation criteria were updated to indicate that all patients in the posttreatment tumor assessment and survival follow-up periods were to be discontinued from the study.</p> <p>The schedule of assessments was updated, including the clarification that HRQoL questionnaires need not be completed. Language was added to clarify that vital signs assessments, laboratory evaluations (hematology chemistry and urinalysis) and physical examinations should follow the local standard of care for patients who remained on study.</p> <p>The safety profile obtained from the interim futility analysis was reviewed and the risk/benefit text was updated to reflect this review.</p>
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported