



Clinical trial results:

A Phase II, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of MEGF0444A Dosed to Progression in Combination with Bevacizumab and FOLFOX in Patients with Previously Untreated Metastatic Colorectal Cancer

Summary

EudraCT number	2011-001867-28
Trial protocol	BE ES PL
Global end of trial date	24 February 2014

Results information

Result version number	v1 (current)
This version publication date	07 August 2016
First version publication date	07 August 2016

Trial information

Trial identification

Sponsor protocol code	MEF4982g
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01399684
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.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	26 September 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	24 February 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This was a Phase II, multicenter, randomized, double-blind, placebo-controlled study. The primary objective was to estimate the efficacy of MEGF0444A combined with modified FOLFOX-6 (mFOLFOX-6; consisting of 5-fluorouracil, folinic acid, oxaliplatin), plus bevacizumab therapy in participants with previously untreated metastatic colorectal cancer (mCRC), as measured by progression-free survival (PFS).

Protection of trial subjects:

The study was conducted in accordance with the United States Food and Drug Administration regulations, the International Conference on Harmonisation E6 guideline for Good Clinical Practice, and applicable local, state, and federal laws, as well as other applicable country laws, according to the regulations and procedures described in the protocol. The investigator, or a person designated by the investigator obtained written informed consent from each participant participating in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. For participants not qualified or incapable of giving legal consent, written consent was obtained from the legally acceptable representative. Approval from the Independent Ethics Committees (IEC) /Institutional Review Board (IRB) was obtained before starting the study. The protocol amendments were prepared by the Sponsor and approved by the IEC/IRB.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 November 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	20 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 18
Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	United States: 41
Country: Number of subjects enrolled	Belgium: 18
Country: Number of subjects enrolled	Spain: 38
Worldwide total number of subjects	126
EEA total number of subjects	67

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)	81
From 65 to 84 years	45
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Overall 127 participants were randomized and included in efficacy analysis, 125 were included in safety analysis (1 participant = screen failure; 1 participant = withdrew prior to first treatment) and 126 participants were randomized in the disposition.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	MEGF0444A + mFOLFOX-6 + Bevacizumab

Arm description:

Participants received MEGF0444A at a fixed dose of 400 milligrams (mg) intravenous (IV) infusion, followed by bevacizumab 5 milligram per kilogram (mg/kg) IV infusion, and then mFOLFOX-6 (consisting of oxaliplatin 85 milligrams per square meter [mg/m^2] IV infusion, 400 mg/m^2 folinic acid IV infusion, and 400 mg/m^2 5-FU administered as an initial IV bolus and followed by continuous IV infusion of 2400 mg/m^2) on Day 1 of each 14-day cycle. After 8 cycles, oxaliplatin was stopped and MEGF0444A, bevacizumab, folinic acid, and 5-FU were continued until disease progression, or unacceptable toxicity for a maximum of 24 months (up to 52 cycles).

Arm type	Experimental
Investigational medicinal product name	MEGF0444A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

MEGF0444A administered at a fixed dose of 400 mg IV infusion on Day 1 of Cycle 1 and on Day 1 of each subsequent 14-day cycle for a maximum of 24 months.

Arm title	Placebo + mFOLFOX-6 + Bevacizumab
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Arm description:

Participants received placebo matched to MEGF0444A at a fixed dose of 400 mg IV infusion, followed by bevacizumab 5 mg/kg IV infusion, and then mFOLFOX-6 (consisting of oxaliplatin 85 mg/m^2 IV infusion, 400 mg/m^2 folinic acid IV infusion, and 400 mg/m^2 5-FU administered as an initial IV bolus and followed by continuous IV infusion of 2400 mg/m^2) on Day 1 of each 14-day cycle. After 8 cycles, oxaliplatin was stopped and placebo matched to MEGF0444A, bevacizumab, folinic acid, and 5-FU were continued until disease progression, or unacceptable toxicity for a maximum of 24 months (up to 52 cycles).

Arm type	Control
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	MEGF0444A + mFOLFOX-6 + Bevacizumab	Placebo + mFOLFOX-6 + Bvacizumab
Started	63	63
Completed	0	0
Not completed	63	63
Consent withdrawn by subject	4	3
Study terminated by Sponsor	41	39
Death	18	21

Baseline characteristics

Reporting groups

Reporting group title	MEGF0444A + mFOLFOX-6 + Bevacizumab
Reporting group description:	
Participants received MEGF0444A at a fixed dose of 400 milligrams (mg) intravenous (IV) infusion, followed by bevacizumab 5 milligram per kilogram (mg/kg) IV infusion, and then mFOLFOX-6 (consisting of oxaliplatin 85 milligrams per square meter [mg/m ²] IV infusion, 400 mg/m ² folinic acid IV infusion, and 400 mg/m ² 5-FU administered as an initial IV bolus and followed by continuous IV infusion of 2400 mg/m ²) on Day 1 of each 14-day cycle. After 8 cycles, oxaliplatin was stopped and MEGF0444A, bevacizumab, folinic acid, and 5-FU were continued until disease progression, or unacceptable toxicity for a maximum of 24 months (up to 52 cycles).	

Reporting group title	Placebo + mFOLFOX-6 + Bevacizumab
Reporting group description:	
Participants received placebo matched to MEGF0444A at a fixed dose of 400 mg IV infusion, followed by bevacizumab 5 mg/kg IV infusion, and then mFOLFOX-6 (consisting of oxaliplatin 85mg/m ² IV infusion, 400 mg/m ² folinic acid IV infusion, and 400 mg/m ² 5-FU administered as an initial IV bolus and followed by continuous IV infusion of 2400 mg/m ²) on Day 1 of each 14-day cycle. After 8 cycles, oxaliplatin was stopped and placebo matched to MEGF0444A, bevacizumab, folinic acid, and 5-FU were continued until disease progression, or unacceptable toxicity for a maximum of 24 months (up to 52 cycles).	

Reporting group values	MEGF0444A + mFOLFOX-6 + Bevacizumab	Placebo + mFOLFOX-6 + Bevacizumab	Total
Number of subjects	63	63	126
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	60.9 ± 10.3	60.9 ± 9.9	-
Gender categorical Units: Subjects			
Female	25	27	52
Male	38	36	74

End points

End points reporting groups

Reporting group title	MEGF0444A + mFOLFOX-6 + Bevacizumab
Reporting group description:	
Participants received MEGF0444A at a fixed dose of 400 milligrams (mg) intravenous (IV) infusion, followed by bevacizumab 5 milligram per kilogram (mg/kg) IV infusion, and then mFOLFOX-6 (consisting of oxaliplatin 85 milligrams per square meter [mg/m ²] IV infusion, 400 mg/m ² folinic acid IV infusion, and 400 mg/m ² 5-FU administered as an initial IV bolus and followed by continuous IV infusion of 2400 mg/m ²) on Day 1 of each 14-day cycle. After 8 cycles, oxaliplatin was stopped and MEGF0444A, bevacizumab, folinic acid, and 5-FU were continued until disease progression, or unacceptable toxicity for a maximum of 24 months (up to 52 cycles).	
Reporting group title	Placebo + mFOLFOX-6 + Bevacizumab
Reporting group description:	
Participants received placebo matched to MEGF0444A at a fixed dose of 400 mg IV infusion, followed by bevacizumab 5 mg/kg IV infusion, and then mFOLFOX-6 (consisting of oxaliplatin 85mg/m ² IV infusion, 400 mg/m ² folinic acid IV infusion, and 400 mg/m ² 5-FU administered as an initial IV bolus and followed by continuous IV infusion of 2400 mg/m ²) on Day 1 of each 14-day cycle. After 8 cycles, oxaliplatin was stopped and placebo matched to MEGF0444A, bevacizumab, folinic acid, and 5-FU were continued until disease progression, or unacceptable toxicity for a maximum of 24 months (up to 52 cycles).	
Subject analysis set title	Placebo + mFOLFOX-6+ Bevacizumab
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
This analysis set included all the participants randomized to placebo part of the study.	

Primary: PFS According to Response Evaluation Criteria in Solid Tumors (RECIST) Version (v)1.1

End point title	PFS According to Response Evaluation Criteria in Solid Tumors (RECIST) Version (v)1.1 ^[1]
End point description:	
PFS was defined as the time from randomization to the first occurrence of documented disease progression (PD) based on RECIST v1.1 or death due to any cause within 30 days of the last treatment, whichever occurs earlier as determined by the investigator. For target lesions, PD was defined as at least a 20 percent (%) increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum of the longest diameter recorded since treatment started or the appearance of 1 or more new lesions. For non-target lesions, PD was defined as the appearance of 1 or more new lesions and/or unequivocal progression of existing non-target lesions. In the event of no disease progression or documented death prior to study termination, PFS was censored at the date of the last evaluable tumor assessment.	
Analysis population: All randomized participants.	
End point type	Primary
End point timeframe:	
Baseline until 20 months	
Notes:	
[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.	
Justification: All the randomized participants were included in the end point analysis.	

End point values	MEGF0444A + mFOLFOX-6 + Bevacizumab	Placebo + mFOLFOX-6+ Bevacizumab		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	63	64		
Units: months				
median (confidence interval 95%)	12 (9.1 to 15.77)	11.9 (9.63 to 15.77)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
The hazard ratio (HR) and 95% confidence interval (CI) was estimated using Cox proportional hazards methodology. The stratification factors used in the analysis were Eastern Cooperative Oncology Group performance status (ECOG PS) (0 vs 1), number of affected organs (1 vs greater than [$>$]1), and adjuvant therapy (yes vs no).	
Comparison groups	MEGF0444A + mFOLFOX-6 + Bevacizumab v Placebo + mFOLFOX-6+ Bevacizumab
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6141
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.149
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.684
upper limit	1.932

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Unstratified analysis.	
Comparison groups	MEGF0444A + mFOLFOX-6 + Bevacizumab v Placebo + mFOLFOX-6+ Bevacizumab
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5475
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.169
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.708
upper limit	1.93

Primary: Percentage of Participants with Disease Progression or Death According to RECIST v1.1

End point title	Percentage of Participants with Disease Progression or Death According to RECIST v1.1 ^{[2][3]}
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End point description:

For target lesions, progressive disease was defined as at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum of the longest diameter recorded since treatment started or the appearance of 1 or more new lesions. For non-target lesions, progressive disease was defined as the appearance of 1 or more new lesions and/or unequivocal progression of existing non-target lesions.

Analysis population: All randomized participants.

End point type	Primary
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End point timeframe:

Baseline until 20 months

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was planned only for PFS duration and reported in respective end points.

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: All the randomized participants were included in the end point analysis.

End point values	MEGF0444A + mFOLFOX-6 + Bevacizumab	Placebo + mFOLFOX-6 + Bevacizumab		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	63	64		
Units: percentage of participants				
number (not applicable)	50.8	46.9		

Statistical analyses

No statistical analyses for this end point

Primary: PFS (Surgery Included) According to RECIST v1.1

End point title	PFS (Surgery Included) According to RECIST v1.1 ^[4]
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End point description:

PFS was defined as the time from randomization to the first occurrence of documented disease progression based on RECIST v1.1 or death due to any cause within 30 days of the last treatment, whichever occurs earlier as determined by the investigator. For target lesions, PD was defined as at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum of the longest diameter recorded since treatment started or the appearance of 1 or more new lesions. For non-target lesions, PD was defined as the appearance of 1 or more new lesions and/or unequivocal progression of existing non-target lesions. In the event of no disease progression or documented death prior to study termination, PFS was censored at the date of the last evaluable tumor assessment.

Analysis population: All randomized participants considered for surgery.

End point type	Primary
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End point timeframe:

Baseline until 20 months

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: All the randomized participants were included in the end point analysis.

End point values	MEGF0444A + mFOLFOX-6 + Bevacizumab	Placebo + mFOLFOX-6+ Bevacizumab		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	63	64		
Units: months				
median (confidence interval 95%)	12.9 (9.26 to 13.77)	12.6 (9.69 to 15.28)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
The HR and 95% CI was estimated using Cox proportional hazards methodology. The stratification factors used in the analysis were ECOG PS (0 vs 1), number of affected organs (1 vs >1), and adjuvant therapy (yes vs no).	
Comparison groups	MEGF0444A + mFOLFOX-6 + Bevacizumab v Placebo + mFOLFOX-6+ Bevacizumab
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7032
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.109
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.837

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Unstratified analysis.	
Comparison groups	MEGF0444A + mFOLFOX-6 + Bevacizumab v Placebo + mFOLFOX-6+ Bevacizumab
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6831
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.107
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.684
upper limit	1.791

Primary: PFS by Baseline Characteristics Used for Stratification

End point title	PFS by Baseline Characteristics Used for Stratification ^[5]
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End point description:

PFS was defined as time from randomization to first occurrence of documented disease progression based on RECIST v1.1 or death due to any cause within 30 days of last treatment, whichever occurs earlier as determined by investigator, and reported according to following baseline risk factors: ECOG PS (0 vs 1), adjuvant therapy (yes vs no), and metastatic sites at enrollment (1 vs > 1). ECOG PS 0 equals (=) to fully active, able to carry on all pre-disease performance without restriction; 1= restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. In event of no disease progression or documented death prior to study termination, PFS was censored at date of the last evaluable tumor assessment.

Analysis population: All randomized participants. '-99999' and '99999' signifies that analyses was not performed due to lack of efficacy and closure of development of molecule.

End point type	Primary
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End point timeframe:

Baseline until 20 months

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: All the randomized participants were included in the end point analysis.

End point values	MEGF0444A + mFOLFOX-6 + Bevacizumab	Placebo + mFOLFOX-6+ Bevacizumab		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	63	64		
Units: months				
median (confidence interval 95%)				
ECOG PS = 0 (n= 30, 36)	13.7 (-99999 to 99999)	11.9 (-99999 to 99999)		
ECOG PS = 1 (n= 33, 28)	9.3 (-99999 to 99999)	11.5 (-99999 to 99999)		
Adjuvant therapy = No (n= 53, 56)	11.6 (-99999 to 99999)	11.9 (-99999 to 99999)		
Adjuvant therapy = Yes (n= 10, 7)	99999 (-99999 to 99999)	14.5 (-99999 to 99999)		
One metastatic site (n= 29, 24)	12.9 (-99999 to 99999)	15.8 (-99999 to 99999)		
Two metastatic sites (n= 34, 39)	11.6 (-99999 to 99999)	9.7 (-99999 to 99999)		

Statistical analyses

Statistical analysis title	Subgroup analysis: ECOG PS = 0
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Statistical analysis description:

The HR and 95% CI was estimated using Cox proportional hazards methodology.

Comparison groups	MEGF0444A + mFOLFOX-6 + Bevacizumab v Placebo + mFOLFOX-6+ Bevacizumab
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Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4498
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.766
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.369
upper limit	1.591

Statistical analysis title	Subgroup analysis: ECOG PS = 1
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Statistical analysis description:

The HR and 95% CI was estimated using Cox proportional hazards methodology.

Comparison groups	MEGF0444A + mFOLFOX-6 + Bevacizumab v Placebo + mFOLFOX-6+ Bevacizumab
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.176
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.655
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.792
upper limit	3.459

Statistical analysis title	Subgroup analysis: Adjuvant therapy = No
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Statistical analysis description:

The HR and 95% CI was estimated using Cox proportional hazards methodology.

Comparison groups	MEGF0444A + mFOLFOX-6 + Bevacizumab v Placebo + mFOLFOX-6+ Bevacizumab
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2761
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.349

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.789
upper limit	2.309

Statistical analysis title	Subgroup analysis: Adjuvant therapy = Yes
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Statistical analysis description:

The HR and 95% CI was estimated using Cox proportional hazards methodology.

Comparison groups	MEGF0444A + mFOLFOX-6 + Bevacizumab v Placebo + mFOLFOX-6+ Bevacizumab
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3078
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.482
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.115
upper limit	2.012

Statistical analysis title	Subgroup analysis: One metastatic site
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Statistical analysis description:

The HR and 95% CI was estimated using Cox proportional hazards methodology.

Comparison groups	MEGF0444A + mFOLFOX-6 + Bevacizumab v Placebo + mFOLFOX-6+ Bevacizumab
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1672
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.763
upper limit	4.88

Statistical analysis title	Subgroup analysis: Two metastatic sites
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Statistical analysis description:

The HR and 95% CI was estimated using Cox proportional hazards methodology.

Comparison groups	MEGF0444A + mFOLFOX-6 + Bevacizumab v Placebo + mFOLFOX-6+ Bevacizumab
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8406
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.512
upper limit	1.725

Primary: PFS (Surgery Included) by Baseline Characteristics Used for Stratification

End point title	PFS (Surgery Included) by Baseline Characteristics Used for Stratification ^[6]
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End point description:

PFS was defined as the time from randomization to the first occurrence of documented disease progression based on RECIST v1.1 or death due to any cause within 30 days of the last treatment, whichever occurs earlier as determined by the investigator, and reported according to the following baseline risk factors: ECOG PS (0 vs 1), adjuvant therapy (yes vs no), and metastatic sites at enrollment (1 vs > 1). ECOG PS 0 = to fully active, able to carry on all pre-disease performance without restriction; 1= restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. In the event of no disease progression or documented death prior to study termination, PFS was censored at the date of the last evaluable tumor assessment.

Analysis population: All randomized participants considered for surgery. '-99999' and '99999' signifies that analyses was not performed due to lack of efficacy and closure of development of molecule.

End point type	Primary
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End point timeframe:

Baseline until 20 months

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: All the randomized participants were included in the end point analysis.

End point values	MEGF0444A + mFOLFOX-6 + Bevacizumab	Placebo + mFOLFOX-6+ Bevacizumab		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	63	64		
Units: months				
median (confidence interval 95%)				
ECOG PS = 0 (n= 30, 36)	13.4 (-99999 to 99999)	12.6 (-99999 to 99999)		
ECOG PS = 1 (n= 33, 28)	9.3 (-99999 to 99999)	99999 (-99999 to 99999)		
Adjuvant therapy = No (n= 53, 56)	12.9 (-99999 to 99999)	12.6 (-99999 to 99999)		
Adjuvant therapy = Yes (n= 10, 7)	13.4 (-99999 to 99999)	14.5 (-99999 to 99999)		

One metastatic site (n= 29, 24)	13 (-99999 to 99999)	15.8 (-99999 to 99999)		
Two metastatic sites (n= 34, 39)	11.6 (-99999 to 99999)	11 (-99999 to 99999)		

Statistical analyses

Statistical analysis title	Subgroup analysis: ECOG PS = 0
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Statistical analysis description:

The HR and 95% CI was estimated using Cox proportional hazards methodology.

Comparison groups	MEGF0444A + mFOLFOX-6 + Bevacizumab v Placebo + mFOLFOX-6+ Bevacizumab
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3547
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.736
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.374
upper limit	1.449

Statistical analysis title	Subgroup analysis: ECOG PS = 1
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Statistical analysis description:

The HR and 95% CI was estimated using Cox proportional hazards methodology.

Comparison groups	MEGF0444A + mFOLFOX-6 + Bevacizumab v Placebo + mFOLFOX-6+ Bevacizumab
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.141
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.728
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.827
upper limit	3.612

Statistical analysis title	Subgroup analysis: Adjuvant therapy = No
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Statistical analysis description:

The HR and 95% CI was estimated using Cox proportional hazards methodology.

Comparison groups	MEGF0444A + mFOLFOX-6 + Bevacizumab v Placebo + mFOLFOX-6+ Bevacizumab
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5021
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.194
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.713
upper limit	2.001

Statistical analysis title

Subgroup analysis: Adjuvant therapy = Yes

Statistical analysis description:

The HR and 95% CI was estimated using Cox proportional hazards methodology.

Comparison groups	MEGF0444A + mFOLFOX-6 + Bevacizumab v Placebo + mFOLFOX-6+ Bevacizumab
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7533
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.803
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.204
upper limit	3.159

Statistical analysis title

Subgroup analysis: One metastatic site

Statistical analysis description:

The HR and 95% CI was estimated using Cox proportional hazards methodology.

Comparison groups	MEGF0444A + mFOLFOX-6 + Bevacizumab v Placebo + mFOLFOX-6+ Bevacizumab
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Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1893
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.764
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.753
upper limit	4.129

Statistical analysis title	Subgroup analysis: Two metastatic sites
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Statistical analysis description:

The HR and 95% CI was estimated using Cox proportional hazards methodology.

Comparison groups	MEGF0444A + mFOLFOX-6 + Bevacizumab v Placebo + mFOLFOX-6+ Bevacizumab
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7037
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.891
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.491
upper limit	1.617

Secondary: Percentage of Participants with Objective Response According to RECIST v1.1

End point title	Percentage of Participants with Objective Response According to RECIST v1.1 ^[7]
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End point description:

Objective response was defined as a complete response (CR) plus partial response (PR), as determined by the investigator using RECIST v1.1. CR was defined as disappearance of all target lesions and PR was defined as at least a 30% decrease in the sum of diameter of target lesions, taking as reference the baseline sum of diameters.

Analysis population: All randomized participants with measurable disease at baseline.

End point type	Secondary
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End point timeframe:

Baseline until 20 months

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: All the randomized participants were included in the end point analysis.

End point values	MEGF0444A + mFOLFOX-6 + Bevacizumab	Placebo + mFOLFOX-6+ Bevacizumab		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	63	63		
Units: percentage of participants				
number (confidence interval 95%)	58.7 (45.6 to 71)	63.5 (51.2 to 75.3)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Unstratified analysis.	
Comparison groups	MEGF0444A + mFOLFOX-6 + Bevacizumab v Placebo + mFOLFOX-6+ Bevacizumab
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7149
Method	Logrank
Parameter estimate	Difference in objective response rate
Point estimate	-4.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.8
upper limit	12.2

Secondary: Duration of Objective Response

End point title	Duration of Objective Response ^[8]
End point description: Duration of objective response was defined as the time from initial occurrence of complete response (CR) or partial response (PR), until documented disease progression using RECIST v1.1 as determined by investigator or death, whichever occurred first. CR was defined as disappearance of all target lesions, and PR was defined as at least a 30% decrease in the sum of diameter of target lesions, taking as reference the baseline sum of diameters in the absence of CR. Participants were censored at the date of last tumor assessment. Duration of response was not analyzed as Sponsor terminated study because of lack of efficacy.	
End point type	Secondary
End point timeframe: Baseline until 20 months	
Notes: [8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: All the randomized participants were included in the end point analysis. However, duration of response was not analyzed as Sponsor terminated study because of lack of efficacy.	

End point values	MEGF0444A + mFOLFOX-6 + Bevacizumab	Placebo + mFOLFOX-6+ Bevacizumab		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	0 ^[9]	0 ^[10]		
Units: months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[9] - Duration of response was not analyzed as Sponsor terminated study because of lack of efficacy.

[10] - Duration of response was not analyzed as Sponsor terminated study because of lack of efficacy.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS) ^[11]
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End point description:

OS is defined as the time from randomization until death from any cause. All deaths were included, without regard to whether they occur on study or following treatment discontinuation. For participants who did not die, OS was censored at the date of last contact.

Analysis population: All randomized participants. '99999' signifies that data was not evaluable due to high number of censored participants.

End point type	Secondary
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End point timeframe:

Baseline until 20 months

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: All the randomized participants were included in the end point analysis.

End point values	MEGF0444A + mFOLFOX-6 + Bevacizumab	Placebo + mFOLFOX-6+ Bevacizumab		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	63	64		
Units: months				
median (confidence interval 95%)	19 (17.28 to 19)	99999 (16.49 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

Unstratified analysis

Comparison groups	MEGF0444A + mFOLFOX-6 + Bevacizumab v Placebo + mFOLFOX-6+ Bevacizumab
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Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.943
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.973
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.456
upper limit	2.074

Statistical analysis title	Statistical Analysis 2
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Statistical analysis description:

The HR and 95% CI was estimated using Cox proportional hazards methodology. The stratification factors used in the analysis were ECOG PS (0 vs 1), number of affected organs (1 vs >1), and adjuvant therapy (yes vs. no).

Comparison groups	MEGF0444A + mFOLFOX-6 + Bevacizumab v Placebo + mFOLFOX-6+ Bevacizumab
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6647
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.838
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.377
upper limit	1.864

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline until 3 years

Adverse event reporting additional description:

Of 127 randomized participants, one participant was screen failure, and one participant was withdrawn prior to first treatment, and therefore 125 randomized participants who received at least one dose of study treatment were included in safety analysis.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.0
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Reporting groups

Reporting group title	MEGF0444A + mFOLFOX-6 + Bevacizumab
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Reporting group description:

Participants received MEGF0444A at a fixed dose of 400 mg IV infusion, followed by bevacizumab 5 mg/kg, IV infusion, and then mFOLFOX-6 (consisting of oxaliplatin 85 mg/m² IV infusion, 400 mg/m² folinic acid IV infusion, and 400 mg/m² 5-FU administered as an initial IV bolus and followed by continuous IV infusion of 2400 mg/m²) on Day 1 of each 14-day cycle. After 8 cycles, oxaliplatin was stopped and MEGF0444A, bevacizumab, folinic acid, and 5-FU were continued until disease progression, or unacceptable toxicity for a maximum of 24 months (up to 52 cycles).

Reporting group title	Placebo + mFOLFOX-6+ Bevacizumab
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Reporting group description:

Participants received placebo matched to MEGF0444A at a fixed dose of 400 mg IV infusion, followed by bevacizumab 5 mg/kg, IV infusion, and then mFOLFOX-6 (consisting of oxaliplatin 85 mg/m² IV infusion, 400 mg/m² folinic acid IV infusion, and 400 mg/m² 5-FU administered as an initial IV bolus and followed by continuous IV infusion of 2400 mg/m²) on Day 1 of each 14-day cycle. After 8 cycles, oxaliplatin was stopped and placebo matched to MEGF0444A, bevacizumab, folinic acid, and 5-FU were continued until disease progression, or unacceptable toxicity for a maximum of 24 months (up to 52 cycles).

Serious adverse events	MEGF0444A + mFOLFOX-6 + Bevacizumab	Placebo + mFOLFOX-6+ Bevacizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 63 (38.10%)	24 / 62 (38.71%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	2 / 63 (3.17%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			

subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic neoplasm			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 63 (0.00%)	3 / 62 (4.84%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (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	1 / 63 (1.59%)	0 / 62 (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	1 / 63 (1.59%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleuritic pain			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax spontaneous			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Body temperature increased			

subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Posterior reversible encephalopathy syndrome			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thalamus haemorrhage			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 63 (0.00%)	2 / 62 (3.23%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	1 / 63 (1.59%)	2 / 62 (3.23%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 63 (0.00%)	2 / 62 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Diarrhoea			
subjects affected / exposed	1 / 63 (1.59%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 63 (1.59%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Enterocutaneous fistula			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal stenosis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal perforation			

subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			

subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle haemorrhage			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal wall abscess			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis suppurative			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			

subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic infection			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal sepsis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative abscess			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 63 (1.59%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	MEGF0444A + mFOLFOX-6 + Bevacizumab	Placebo + mFOLFOX-6+ Bevacizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	62 / 63 (98.41%)	62 / 62 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	18 / 63 (28.57%)	21 / 62 (33.87%)	
occurrences (all)	27	29	
Deep vein thrombosis			
subjects affected / exposed	1 / 63 (1.59%)	5 / 62 (8.06%)	
occurrences (all)	1	5	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	31 / 63 (49.21%)	28 / 62 (45.16%)	
occurrences (all)	60	41	
Mucosal inflammation			
subjects affected / exposed	24 / 63 (38.10%)	29 / 62 (46.77%)	
occurrences (all)	44	59	
Asthenia			
subjects affected / exposed	24 / 63 (38.10%)	18 / 62 (29.03%)	
occurrences (all)	45	46	
Pyrexia			
subjects affected / exposed	9 / 63 (14.29%)	11 / 62 (17.74%)	
occurrences (all)	15	15	
Temperature intolerance			
subjects affected / exposed	7 / 63 (11.11%)	5 / 62 (8.06%)	
occurrences (all)	8	5	
Oedema peripheral			
subjects affected / exposed	5 / 63 (7.94%)	6 / 62 (9.68%)	
occurrences (all)	5	9	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	28 / 63 (44.44%)	25 / 62 (40.32%)	
occurrences (all)	50	36	

Dysphonia subjects affected / exposed occurrences (all)	8 / 63 (12.70%) 12	12 / 62 (19.35%) 18	
Dyspnoea subjects affected / exposed occurrences (all)	10 / 63 (15.87%) 16	9 / 62 (14.52%) 17	
Rhinorrhoea subjects affected / exposed occurrences (all)	6 / 63 (9.52%) 9	5 / 62 (8.06%) 7	
Oropharyngeal pain subjects affected / exposed occurrences (all)	4 / 63 (6.35%) 5	6 / 62 (9.68%) 6	
Cough subjects affected / exposed occurrences (all)	6 / 63 (9.52%) 6	2 / 62 (3.23%) 2	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	10 / 63 (15.87%) 10	9 / 62 (14.52%) 10	
Depression subjects affected / exposed occurrences (all)	3 / 63 (4.76%) 7	6 / 62 (9.68%) 6	
Investigations Weight decreased subjects affected / exposed occurrences (all)	10 / 63 (15.87%) 16	4 / 62 (6.45%) 4	
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	4 / 63 (6.35%) 5	1 / 62 (1.61%) 4	
Nervous system disorders Dysaesthesia subjects affected / exposed occurrences (all)	15 / 63 (23.81%) 38	21 / 62 (33.87%) 44	
Neuropathy peripheral subjects affected / exposed occurrences (all)	17 / 63 (26.98%) 23	18 / 62 (29.03%) 30	

Dysgeusia			
subjects affected / exposed	17 / 63 (26.98%)	16 / 62 (25.81%)	
occurrences (all)	31	26	
Headache			
subjects affected / exposed	15 / 63 (23.81%)	14 / 62 (22.58%)	
occurrences (all)	22	23	
Paraesthesia			
subjects affected / exposed	10 / 63 (15.87%)	9 / 62 (14.52%)	
occurrences (all)	13	19	
Neurotoxicity			
subjects affected / exposed	10 / 63 (15.87%)	7 / 62 (11.29%)	
occurrences (all)	18	14	
Dizziness			
subjects affected / exposed	7 / 63 (11.11%)	9 / 62 (14.52%)	
occurrences (all)	8	11	
Peripheral sensory neuropathy			
subjects affected / exposed	8 / 63 (12.70%)	8 / 62 (12.90%)	
occurrences (all)	11	11	
Polyneuropathy			
subjects affected / exposed	8 / 63 (12.70%)	7 / 62 (11.29%)	
occurrences (all)	25	16	
Hypoaesthesia			
subjects affected / exposed	5 / 63 (7.94%)	4 / 62 (6.45%)	
occurrences (all)	7	4	
Lethargy			
subjects affected / exposed	2 / 63 (3.17%)	5 / 62 (8.06%)	
occurrences (all)	3	9	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	18 / 63 (28.57%)	20 / 62 (32.26%)	
occurrences (all)	28	30	
Anaemia			
subjects affected / exposed	8 / 63 (12.70%)	10 / 62 (16.13%)	
occurrences (all)	14	15	
Thrombocytopenia			

subjects affected / exposed occurrences (all)	4 / 63 (6.35%) 8	3 / 62 (4.84%) 5	
Eye disorders Lacrimation increased subjects affected / exposed occurrences (all)	5 / 63 (7.94%) 5	3 / 62 (4.84%) 3	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	43 / 63 (68.25%) 92	39 / 62 (62.90%) 96	
Nausea subjects affected / exposed occurrences (all)	40 / 63 (63.49%) 72	41 / 62 (66.13%) 81	
Constipation subjects affected / exposed occurrences (all)	23 / 63 (36.51%) 48	27 / 62 (43.55%) 45	
Vomiting subjects affected / exposed occurrences (all)	21 / 63 (33.33%) 43	18 / 62 (29.03%) 39	
Abdominal pain subjects affected / exposed occurrences (all)	18 / 63 (28.57%) 23	17 / 62 (27.42%) 24	
Stomatitis subjects affected / exposed occurrences (all)	14 / 63 (22.22%) 24	14 / 62 (22.58%) 30	
Abdominal pain upper subjects affected / exposed occurrences (all)	11 / 63 (17.46%) 20	12 / 62 (19.35%) 19	
Dyspepsia subjects affected / exposed occurrences (all)	6 / 63 (9.52%) 6	9 / 62 (14.52%) 12	
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	4 / 63 (6.35%) 5	5 / 62 (8.06%) 5	
Oral pain			

subjects affected / exposed	4 / 63 (6.35%)	5 / 62 (8.06%)	
occurrences (all)	4	5	
Gingival bleeding			
subjects affected / exposed	3 / 63 (4.76%)	5 / 62 (8.06%)	
occurrences (all)	7	8	
Toothache			
subjects affected / exposed	4 / 63 (6.35%)	4 / 62 (6.45%)	
occurrences (all)	5	7	
Abdominal distension			
subjects affected / exposed	5 / 63 (7.94%)	1 / 62 (1.61%)	
occurrences (all)	5	1	
Haemorrhoids			
subjects affected / exposed	5 / 63 (7.94%)	1 / 62 (1.61%)	
occurrences (all)	6	1	
Proctalgia			
subjects affected / exposed	4 / 63 (6.35%)	2 / 62 (3.23%)	
occurrences (all)	4	5	
Flatulence			
subjects affected / exposed	1 / 63 (1.59%)	4 / 62 (6.45%)	
occurrences (all)	1	4	
Rectal haemorrhage			
subjects affected / exposed	4 / 63 (6.35%)	0 / 62 (0.00%)	
occurrences (all)	4	0	
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	8 / 63 (12.70%)	13 / 62 (20.97%)	
occurrences (all)	16	23	
Rash			
subjects affected / exposed	8 / 63 (12.70%)	13 / 62 (20.97%)	
occurrences (all)	14	20	
Alopecia			
subjects affected / exposed	9 / 63 (14.29%)	9 / 62 (14.52%)	
occurrences (all)	12	12	
Dry skin			

subjects affected / exposed	9 / 63 (14.29%)	6 / 62 (9.68%)	
occurrences (all)	11	6	
Nail disorder			
subjects affected / exposed	6 / 63 (9.52%)	4 / 62 (6.45%)	
occurrences (all)	6	7	
Pruritus			
subjects affected / exposed	4 / 63 (6.35%)	5 / 62 (8.06%)	
occurrences (all)	5	5	
Skin hyperpigmentation			
subjects affected / exposed	7 / 63 (11.11%)	3 / 62 (4.84%)	
occurrences (all)	7	3	
Rash erythematous			
subjects affected / exposed	1 / 63 (1.59%)	4 / 62 (6.45%)	
occurrences (all)	2	4	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	7 / 63 (11.11%)	10 / 62 (16.13%)	
occurrences (all)	10	11	
Dysuria			
subjects affected / exposed	5 / 63 (7.94%)	6 / 62 (9.68%)	
occurrences (all)	5	7	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	12 / 63 (19.05%)	10 / 62 (16.13%)	
occurrences (all)	13	11	
Back pain			
subjects affected / exposed	11 / 63 (17.46%)	10 / 62 (16.13%)	
occurrences (all)	16	15	
Pain in extremity			
subjects affected / exposed	6 / 63 (9.52%)	10 / 62 (16.13%)	
occurrences (all)	6	12	
Musculoskeletal pain			
subjects affected / exposed	6 / 63 (9.52%)	8 / 62 (12.90%)	
occurrences (all)	6	9	
Muscle spasms			

subjects affected / exposed occurrences (all)	5 / 63 (7.94%) 7	4 / 62 (6.45%) 6	
Myalgia subjects affected / exposed occurrences (all)	6 / 63 (9.52%) 7	3 / 62 (4.84%) 5	
Pain in jaw subjects affected / exposed occurrences (all)	3 / 63 (4.76%) 3	4 / 62 (6.45%) 5	
Infections and infestations			
Upper respiratory tract infection subjects affected / exposed occurrences (all)	6 / 63 (9.52%) 7	11 / 62 (17.74%) 15	
Urinary tract infection subjects affected / exposed occurrences (all)	8 / 63 (12.70%) 11	9 / 62 (14.52%) 11	
Nasopharyngitis subjects affected / exposed occurrences (all)	11 / 63 (17.46%) 13	4 / 62 (6.45%) 6	
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	18 / 63 (28.57%) 36	24 / 62 (38.71%) 32	
Hypokalemia subjects affected / exposed occurrences (all)	5 / 63 (7.94%) 6	6 / 62 (9.68%) 7	
Hypomagnesaemia subjects affected / exposed occurrences (all)	5 / 63 (7.94%) 6	1 / 62 (1.61%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 October 2011	<ul style="list-style-type: none">- Clarified several aspects of study conduct and background;- FOLFOX dose modification schema for participants experiencing hematologic toxicity was modified to reflect prevailing practices;-The use of head computed tomography or brain magnetic resonance imaging was pertained only to participants with suspected central nervous system metastases or carcinomatous meningitis.
18 September 2012	<ul style="list-style-type: none">- Included new unplanned safety data from Study MEF4984g (a Phase II study of MEGF0444A, bevacizumab, and carboplatin/paclitaxel chemotherapy in advanced non-small cell lung cancer participants) and from the current Study MEF4982g. As a result of these analyses, any Grade greater than or equal to (\geq) 3 bleeding adverse event was reported within 24 hours as a protocol-defined adverse event of special interest. Concomitant use of non-steroidal anti-inflammatory drugs was discouraged;- Included clinical safety and efficacy updates from the Phase 1 studies of MEGF0444A;- Included the required use of in-line filter for administration of MEGF0444A.
21 April 2013	<ul style="list-style-type: none">- The Sponsor's plan to perform an interim analysis was added. The interim analysis was intended to provide a preliminary assessment of the activity of study regimen and not to terminate the trial if efficacy results appeared favourable;- The amendment clarified that only participants who discontinued study treatment for reasons other than disease progression continued tumor assessments until documentation of progressive disease, initiation of another anti-cancer therapy, withdrawal of consent, or death.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The protocol-specified primary analysis demonstrated no evidence of efficacy; and the Sponsor terminated the study.

Notes: