



Clinical trial results:

A Randomized, Phase III, Multicenter, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Onartuzumab (MetMAb) in Combination with 5-Fluorouracil, Folinic Acid, and Oxaliplatin (mFOLFOX6) in Patients with Metastatic HER2-Negative, MET-Positive Gastroesophageal Cancer

Summary

EudraCT number	2012-001402-23
Trial protocol	ES IT BE GB DE CZ PL
Global end of trial date	15 December 2015

Results information

Result version number	v1 (current)
This version publication date	29 December 2016
First version publication date	29 December 2016

Trial information

Trial identification

Sponsor protocol code	YO28322
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01662869
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	F.Hoffmann-La Roche Ltd., Roche Trial Information Hotline, 41 61 6878333, global.trial_information@roche.com
Scientific contact	F.Hoffmann-La Roche Ltd., Roche Trial Information Hotline, 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	15 December 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	15 December 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This is a Phase III, randomized, placebo-controlled, double-blind study which evaluates the efficacy and safety of onartuzumab + mFOLFOX6 compared with placebo + mFOLFOX6 as measured by overall survival (OS) in participants with previously untreated human epidermal growth factor receptor 2 (HER2)-negative metastatic gastroesophageal cancer (GEC) classified as Met-immunohistochemistry (IHC) 2 + or 3 + (Met 2 + /3 + subgroup), and Met-IHC 1 + , 2 + , or 3 + (intent-to-treat [ITT] population).

Protection of trial subjects:

This study was conducted in full conformance with the International Conference on Harmonisation (ICH) E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study complied with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 November 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
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	Poland: 31
Country: Number of subjects enrolled	Spain: 50
Country: Number of subjects enrolled	United Kingdom: 35
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	Czech Republic: 13
Country: Number of subjects enrolled	France: 33
Country: Number of subjects enrolled	Germany: 27
Country: Number of subjects enrolled	Italy: 62
Country: Number of subjects enrolled	Hong Kong: 6
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 115
Country: Number of subjects enrolled	Malaysia: 2
Country: Number of subjects enrolled	Singapore: 2
Country: Number of subjects enrolled	Thailand: 29
Country: Number of subjects enrolled	Taiwan: 22

Country: Number of subjects enrolled	Australia: 16
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Guatemala: 3
Country: Number of subjects enrolled	Israel: 5
Country: Number of subjects enrolled	Mexico: 11
Country: Number of subjects enrolled	Russian Federation: 28
Country: Number of subjects enrolled	Switzerland: 5
Country: Number of subjects enrolled	Turkey: 27
Country: Number of subjects enrolled	United States: 27
Worldwide total number of subjects	563
EEA total number of subjects	260

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)	373
From 65 to 84 years	190
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Five hundred and sixty-three participants were enrolled in the study and received treatment with onartuzumab or placebo in combination with mFOLFOX6.

Period 1

Period 1 title	Overall Trial (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	Placebo + mFOLFOX6

Arm description:

Placebo matched to onartuzumab was administered by intravenous (IV) infusion (first infusion for 60 minutes, and subsequently for 30 minutes) on Day 1 of each 14-day cycle followed by mFOLFOX6 regimen comprising of oxaliplatin 85 milligrams per meter square (mg/m^2) IV, folinic acid ($400 \text{ mg}/\text{m}^2$) or levofolinic acid ($200 \text{ mg}/\text{m}^2$) or as deemed appropriate per investigator and 5-fluorouracil (5-FU) $400 \text{ mg}/\text{m}^2$ IV bolus, then 5-FU $2400 \text{ mg}/\text{m}^2$ continuous IV infusion over 46 to 48 hours until 12 cycles. Participants without disease progression after 12 cycles of mFOLFOX6 with placebo, further continued treatment with placebo until disease progression, unacceptable toxicity, or death.

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

Dosage and administration details:

Placebo matched to onartuzumab was administered by IV infusion.

Arm title	Onartuzumab + mFOLFOX6
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Arm description:

Onartuzumab $10 \text{ mg}/\text{kilogram}$ (mg/kg) in 250 milliliter (mL) final 0.9% normal saline solution (NSS) was administered by IV infusion (first infusion for 60 minutes, and subsequently for 30 minutes) on Day 1 of each 14-day cycle followed by mFOLFOX6 regimen comprising of oxaliplatin $85 \text{ mg}/\text{m}^2$ IV, folinic acid ($400 \text{ mg}/\text{m}^2$) or levofolinic acid ($200 \text{ mg}/\text{m}^2$) or as deemed appropriate per investigator and 5-FU $400 \text{ mg}/\text{m}^2$ IV bolus, then 5-FU $2400 \text{ mg}/\text{m}^2$ continuous IV infusion over 46 to 48 hours until 12 cycles. Participants without disease progression after 12 cycles of mFOLFOX6 with onartuzumab, further continued treatment with onartuzumab until disease progression, unacceptable toxicity, or death.

Arm type	Experimental
Investigational medicinal product name	Onartuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Onartuzumab in NSS was administered by IV infusion.

Number of subjects in period 1	Placebo + mFOLFOX6	Onartuzumab + mFOLFOX6
Started	283	280
Completed	0	0
Not completed	283	280
Consent withdrawn by subject	24	18
Physician decision	-	1
Study terminated by Sponsor	82	79
Death	159	164
Unspecified	8	7
Lost to follow-up	8	9
Randomized, not treated	2	2

Baseline characteristics

Reporting groups

Reporting group title	Placebo + mFOLFOX6
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Reporting group description:

Placebo matched to onartuzumab was administered by intravenous (IV) infusion (first infusion for 60 minutes, and subsequently for 30 minutes) on Day 1 of each 14-day cycle followed by mFOLFOX6 regimen comprising of oxaliplatin 85 milligrams per meter square (mg/m^2) IV, folinic acid ($400 \text{ mg}/\text{m}^2$) or levofolinic acid ($200 \text{ mg}/\text{m}^2$) or as deemed appropriate per investigator and 5-fluorouracil (5-FU) $400 \text{ mg}/\text{m}^2$ IV bolus, then 5-FU $2400 \text{ mg}/\text{m}^2$ continuous IV infusion over 46 to 48 hours until 12 cycles. Participants without disease progression after 12 cycles of mFOLFOX6 with placebo, further continued treatment with placebo until disease progression, unacceptable toxicity, or death.

Reporting group title	Onartuzumab + mFOLFOX6
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Reporting group description:

Onartuzumab 10 mg/kilogram (mg/kg) in 250 milliliter (mL) final 0.9% normal saline solution (NSS) was administered by IV infusion (first infusion for 60 minutes, and subsequently for 30 minutes) on Day 1 of each 14-day cycle followed by mFOLFOX6 regimen comprising of oxaliplatin $85 \text{ mg}/\text{m}^2$ IV, folinic acid ($400 \text{ mg}/\text{m}^2$) or levofolinic acid ($200 \text{ mg}/\text{m}^2$) or as deemed appropriate per investigator and 5-FU $400 \text{ mg}/\text{m}^2$ IV bolus, then 5-FU $2400 \text{ mg}/\text{m}^2$ continuous IV infusion over 46 to 48 hours until 12 cycles. Participants without disease progression after 12 cycles of mFOLFOX6 with onartuzumab, further continued treatment with onartuzumab until disease progression, unacceptable toxicity, or death.

Reporting group values	Placebo + mFOLFOX6	Onartuzumab + mFOLFOX6	Total
Number of subjects	283	280	563
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	57.7	58.7	
standard deviation	± 12.2	± 11.4	-
Gender categorical			
Units: Subjects			
Female	100	91	191
Male	183	189	372

End points

End points reporting groups

Reporting group title	Placebo + mFOLFOX6
Reporting group description:	
Placebo matched to onartuzumab was administered by intravenous (IV) infusion (first infusion for 60 minutes, and subsequently for 30 minutes) on Day 1 of each 14-day cycle followed by mFOLFOX6 regimen comprising of oxaliplatin 85 milligrams per meter square (mg/m ²) IV, folinic acid (400 mg/m ²) or levofolinic acid (200 mg/m ²) or as deemed appropriate per investigator and 5-fluorouracil (5-FU) 400 mg/m ² IV bolus, then 5-FU 2400 mg/m ² continuous IV infusion over 46 to 48 hours until 12 cycles. Participants without disease progression after 12 cycles of mFOLFOX6 with placebo, further continued treatment with placebo until disease progression, unacceptable toxicity, or death.	
Reporting group title	Onartuzumab + mFOLFOX6
Reporting group description:	
Onartuzumab 10 mg/kilogram (mg/kg) in 250 milliliter (mL) final 0.9% normal saline solution (NSS) was administered by IV infusion (first infusion for 60 minutes, and subsequently for 30 minutes) on Day 1 of each 14-day cycle followed by mFOLFOX6 regimen comprising of oxaliplatin 85 mg/m ² IV, folinic acid (400 mg/m ²) or levofolinic acid (200 mg/m ²) or as deemed appropriate per investigator and 5-FU 400 mg/m ² IV bolus, then 5-FU 2400 mg/m ² continuous IV infusion over 46 to 48 hours until 12 cycles. Participants without disease progression after 12 cycles of mFOLFOX6 with onartuzumab, further continued treatment with onartuzumab until disease progression, unacceptable toxicity, or death.	

Primary: Percentage of Participants Who Died: Met 2 + /3 + Subgroup GEC Participants

End point title	Percentage of Participants Who Died: Met 2 + /3 + Subgroup GEC Participants ^[1]
End point description:	
Met 2+ /3+ subgroup included all randomized participants with previously untreated HER2-negative GEC classified as Met-IHC 2+ or 3+.	
End point type	Primary
End point timeframe:	
Randomization until death due to any cause (up to approximately 1.5 years)	
Notes:	
[1] - 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 section is not applicable for this end point.	

End point values	Placebo + mFOLFOX6	Onartuzumab + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	105		
Units: Percentage of participants				
number (not applicable)	37.6	33.3		

Statistical analyses

No statistical analyses for this end point

Primary: OS: Met 2 + /3 + Subgroup GEC Participants

End point title	OS: Met 2 + /3 + Subgroup GEC Participants
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End point description:

OS was defined as the time from randomization to death due to any cause. Data for participants who were not reported as having died at the time of analysis were censored at the date they were last known to be alive. Participants who do not have post-baseline information were censored at the date of randomization plus 1 day. OS was estimated using Kaplan-Meier methodology. 99999 refers to the upper limit of confidence interval (CI) which was not-estimable due to insufficient follow-up. Met 2+/3+ subgroup population.

End point type	Primary
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End point timeframe:

Baseline until death due to any cause (up to approximately 1.5 years)

End point values	Placebo + mFOLFOX6	Onartuzumab + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	105		
Units: Months				
median (confidence interval 95%)	9.66 (7.72 to 99999)	11.04 (8.94 to 12.09)		

Statistical analyses

Statistical analysis title	Stratified Analysis
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Statistical analysis description:

Hazard ratios were estimated by Cox regression. The stratification factors are Met expression (level I, II, III, IV, or V), world region (Asia-Pacific vs. other), and prior gastrectomy (yes vs. no).

Comparison groups	Placebo + mFOLFOX6 v Onartuzumab + mFOLFOX6
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0311 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	1.03

Notes:

[2] - One-sided p-value

Statistical analysis title	Unstratified Analysis
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Statistical analysis description:

Hazard ratios were estimated by Cox regression.

Comparison groups	Placebo + mFOLFOX6 v Onartuzumab + mFOLFOX6
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Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1955 ^[3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	1.29

Notes:

[3] - One-sided p-value

Primary: Percentage of Participants Who Died: ITT Population

End point title	Percentage of Participants Who Died: ITT Population ^[4]
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End point description:

ITT population included all randomized participants. Here, "Number of subjects analysed" indicates the total number of participants who provided evaluable data for this endpoint.

End point type	Primary
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End point timeframe:

Baseline until death due to any cause (up to approximately 1.5 years)

Notes:

[4] - 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 section is not applicable for this end point.

End point values	Placebo + mFOLFOX6	Onartuzumab + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	283	279		
Units: Percentage of participants				
number (not applicable)	26.1	25.8		

Statistical analyses

No statistical analyses for this end point

Primary: OS: ITT Population

End point title	OS: ITT Population
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End point description:

OS was defined as the time from randomization to death due to any cause. Data for participants who were not reported as having died at the time of analysis were censored at the date they were last known to be alive. Participants who do not have post-baseline information were censored at the date of randomization plus 1 day. OS was estimated using Kaplan-Meier methodology. 99999 refers to the upper limit of CI which was not-estimable due to insufficient follow-up. ITT population. Here, "Number of subjects analysed" indicates the total number of participants who provided evaluable data for this endpoint.

End point type	Primary
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End point timeframe:

Baseline until death due to any cause (up to approximately 1.5 years)

End point values	Placebo + mFOLFOX6	Onartuzumab + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	283	279		
Units: Months				
median (confidence interval 95%)	11.33 (9.59 to 99999)	11.04 (9.95 to 13.63)		

Statistical analyses

Statistical analysis title	Stratified Analysis
Statistical analysis description:	
Hazard ratios were estimated by Cox regression. The stratification factors are Met expression (level I, II, III, IV, or V), world region (Asia-Pacific vs. other), and prior gastrectomy (yes vs. no).	
Comparison groups	Onartuzumab + mFOLFOX6 v Placebo + mFOLFOX6
Number of subjects included in analysis	562
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1222 ^[5]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	1.15

Notes:

[5] - One-sided p-value

Statistical analysis title	Unstratified Analysis
Statistical analysis description:	
Hazard ratios were estimated by Cox regression.	
Comparison groups	Placebo + mFOLFOX6 v Onartuzumab + mFOLFOX6
Number of subjects included in analysis	562
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3899 ^[6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.32

Notes:

[6] - One-sided p-value

Secondary: Progression-free survival (PFS) as Determined by Investigator Using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1): Met 2 + /3 + Subgroup GEC Participants

End point title	Progression-free survival (PFS) as Determined by Investigator Using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1): Met 2 + /3 + Subgroup GEC Participants
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End point description:

PFS is defined as the time between the date of randomization and the date of first documented disease progression (PD) or death, whichever occurs first. Participants who were alive and have not experienced PD at the time of analysis were censored at the time of the last tumor assessment. Participants with no post-baseline tumor assessment were censored at the randomization date plus 1 day. PD: at least 20% increase in the sum of diameters of target lesions compared to the smallest sum of diameters on-study and absolute increase of at least 5 millimeters (mm), progression of existing non-target lesions, or presence of new lesions. As per protocol, the secondary efficacy endpoints (including patient-reported endpoints) were only to be analyzed if the primary outcome results in statistical significance. As the pre-specified criteria was not met, the analysis was not performed.

End point type	Secondary
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End point timeframe:

Baseline up to disease progression or death due to any cause, whichever occurred first (up to approximately 1.5 years)

End point values	Placebo + mFOLFOX6	Onartuzumab + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[7]	0 ^[8]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[7] - As the pre-specified criteria was not met, the analysis was not performed.

[8] - As the pre-specified criteria was not met, the analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: PFS as Determined by Investigator Using RECIST v1.1: ITT Population

End point title	PFS as Determined by Investigator Using RECIST v1.1: ITT Population
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End point description:

PFS is defined as the time between the date of randomization and the date of first documented PD or death, whichever occurs first. Participants who were alive and have not experienced PD at the time of analysis were censored at the time of the last tumor assessment. Participants with no post-baseline tumor assessment were censored at the randomization date plus 1 day. PD: at least 20% increase in the sum of diameters of target lesions compared to the smallest sum of diameters on-study and absolute increase of at least 5 mm, progression of existing non-target lesions, or presence of new lesions. As per protocol, the secondary efficacy endpoints (including patient-reported endpoints) were only to be

analyzed if the primary outcome results in statistical significance. As the pre-specified criteria was not met, the analysis was not performed.

End point type	Secondary
End point timeframe:	
Baseline up to disease progression or death due to any cause, whichever occurred first (up to approximately 3 years)	

End point values	Placebo + mFOLFOX6	Onartuzumab + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[9]	0 ^[10]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[9] - As the pre-specified criteria was not met, the analysis was not performed.

[10] - As the pre-specified criteria was not met, the analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Objective Response as Determined Using RECIST v1.1: Met 2 + /3 + Subgroup GEC Participants

End point title	Percentage of Participants With Objective Response as Determined Using RECIST v1.1: Met 2 + /3 + Subgroup GEC Participants
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End point description:

Objective response:complete response(CR) or partial response(PR) as determined by the Investigator using RECIST v1.1 on 2 consecutive occasions at least 6 weeks apart.Participants were assessed by computed tomography (CT) or magnetic resonance imaging (MRI).CR:complete disappearance of all target lesions&non-target disease,except nodal disease.All nodes,both target and non-target,must decrease to normal (short axis less than [$<$] 10 millimeter [mm]).No new lesions.PR:greater than or equal(\geq)30% decrease from baseline in the sum of diameters of target lesions.The short axis was used in the sum for target nodes,while the longest diameter was used in the sum for all other target lesions.No unequivocal progression of non-target disease.No new lesions.As per protocol,the secondary efficacy endpoints(including patient-reported endpoint)were only to be analyzed if the primary outcome results in statistical significance.As the pre-specified criteria was not met,the analysis was not

End point type	Secondary
End point timeframe:	
Baseline up to disease progression or death due to any cause, whichever occurred first (up to approximately 1.5 years)	

Statistical analyses

Secondary: Percentage of Participants With Objective Response as Determined Using RECIST v1.1: ITT Population

End point title	Percentage of Participants With Objective Response as Determined Using RECIST v1.1: ITT Population
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End point description:

Objective response is defined as a CR or PR as determined by the Investigator using RECIST v1.1 on 2 consecutive occasions at least 6 weeks apart. Participants were evaluated for tumor response for target lesions and assessed by CT or MRI. CR was defined as complete disappearance of all target lesions and non-target disease, with the exception of nodal disease. All nodes, both target and non-target, must decrease to normal (short axis <10 mm). No new lesions. PR was defined as $\geq 30\%$ decrease from baseline in the sum of diameters of target lesions. The short axis was used in the sum for target nodes, while the longest diameter was used in the sum for all other target lesions. No unequivocal progression of non-target disease. No new lesions. As per protocol, the secondary efficacy endpoints (including patient-reported endpoints) were only to be analyzed if the primary outcome results in statistical significance. As the pre-specified criteria was not met, the analysis was not performed.

End point type	Secondary
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End point timeframe:

Baseline up to disease progression or death due to any cause, whichever occurred first (up to approximately 1.5 years)

End point values	Placebo + mFOLFOX6	Onartuzumab + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[11]	0 ^[12]		
Units: Percentage of participants				
number (not applicable)				

Notes:

[11] - As the pre-specified criteria was not met, the analysis was not performed.

[12] - As the pre-specified criteria was not met, the analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Disease Control as Determined Using RECIST v1.1: Met 2 + /3 + Subgroup GEC Participants

End point title	Percentage of Participants With Disease Control as Determined Using RECIST v1.1: Met 2 + /3 + Subgroup GEC Participants
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End point description:

Disease Control: Participants with CR, PR or stable disease(SD)for at least 6 weeks by RECIST v1.1. CR: complete disappearance of all target lesions&non-target disease,except nodal disease. All nodes must decrease to normal.PR: $\geq 30\%$ decrease from baseline in the sum of diameters of target lesions.The short axis was used in the sum for target nodes&the longest diameter was used in the sum for all other target lesions.No unequivocal progression of non-target disease. SD:neither sufficient shrinkage nor increase to qualify for PR or PD.PD:at least 20% increase in the sum of diameters of target lesions compared to the smallest sum of diameters on-study and absolute increase of at least 5 mm,progression of existing non-target lesions,or new lesions.As per protocol,the secondary efficacy endpoints (including patient-reported endpoints)were only to be analyzed if the primary outcome results in statistical significance.As the pre-specified criteria was not met,the analysis was not performed.

End point type	Secondary
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End point timeframe:

Baseline up to disease progression or death due to any cause, whichever occurred first (up to approximately 1.5 years)

End point values	Placebo + mFOLFOX6	Onartuzumab + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[13]	0 ^[14]		
Units: Percentage of participants				
number (not applicable)				

Notes:

[13] - As the pre-specified criteria was not met, the analysis was not performed.

[14] - As the pre-specified criteria was not met, the analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Disease Control as Determined Using RECIST v1.1: ITT Population

End point title	Percentage of Participants With Disease Control as Determined Using RECIST v1.1: ITT Population
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End point description:

Disease control: Participants with CR, PR or SD for at least 6 weeks by RECIST v1.1. CR: complete disappearance of all target lesions & non-target disease, except nodal disease. All nodes must decrease to normal. PR: $\geq 30\%$ decrease from baseline in the sum of diameters of target lesions. The short axis was used in the sum for target nodes & the longest diameter was used in the sum for all other target lesions. No unequivocal progression of non-target disease. SD: neither sufficient shrinkage nor increase to qualify for PR or PD. PD: at least 20% increase in the sum of diameters of target lesions compared to the smallest sum of diameters on-study and absolute increase of at least 5 mm, progression of existing non-target lesions, or new lesions. As per protocol, the secondary efficacy endpoints (including patient-reported endpoints) were only to be analyzed if the primary outcome results in statistical significance. As the pre-specified criteria was not met, the analysis was not performed

End point type	Secondary
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End point timeframe:

Baseline up to disease progression or death due to any cause, whichever occurred first (up to approximately 1.5 years)

End point values	Placebo + mFOLFOX6	Onartuzumab + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[15]	0 ^[16]		
Units: Percentage of participants				
number (not applicable)				

Notes:

[15] - As the pre-specified criteria was not met, the analysis was not performed.

[16] - As the pre-specified criteria was not met, the analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Percentage of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)
End point description:	
An AE was considered any unfavorable and unintended sign, symptom, or disease associated with the use of the study drug, whether or not considered related to the study drug. Preexisting conditions that worsened during the study were reported as adverse events. SAE is any experience that suggests a significant hazard, contraindication, side effect or precaution that: results in death, is life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or is medically significant. AEs included both serious as well as non-serious adverse events. Safety population included all randomized participants who received at least one dose of study treatment.	
End point type	Secondary
End point timeframe:	
Baseline up to 30 days after the last administration of study drug (approximately up to 3 years)	

End point values	Placebo + mFOLFOX6	Onartuzumab + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	280	279		
Units: Percentage of participants				
number (not applicable)				
AEs	97.9	98.9		
SAEs	33.9	39.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Anti-Therapeutic Antibodies (ATAs) Against Onartuzumab

End point title	Percentage of Participants With Anti-Therapeutic Antibodies (ATAs) Against Onartuzumab
End point description:	
Safety population. Here, "Number of subjects analysed" indicates the total number of participants who provided evaluable data for this endpoint and "n" indicates total number of participants with evaluable data for a particular time point.	
End point type	Secondary
End point timeframe:	
Pre-dose (within 1 hour before infusion start) on Day 1 of Cycles 1 and 4, (cycle length = 14 days), at study drug discontinuation visit (up to 3 years)	

End point values	Placebo + mFOLFOX6	Onartuzumab + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	62		
Units: Percentage of participants				
number (not applicable)				
Baseline (n= 50, 62)	3	4		

Post-baseline (n= 50, 56)	4	2		
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Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Observed Serum Onartuzumab Concentration (Cmin)

End point title	Minimum Observed Serum Onartuzumab Concentration
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End point description:

Safety population. "Number of subjects analysed" indicates the total number of participants who provided evaluable data for this endpoint.

End point type	Secondary
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End point timeframe:

Predose (0-1 hours) on Day 1 of Cycles 1, 2 and 4 (cycle length = 14 days), at study drug discontinuation visit (up to approximately 1.5 years)

Notes:

[17] - 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: Only participants who received onartuzumab were included in analysis; hence only Onartuzumab + mFOLFOX6 arm is reported.

End point values	Onartuzumab + mFOLFOX6			
Subject group type	Reporting group			
Number of subjects analysed	194			
Units: micrograms per milliliter (mcg/mL)				
geometric mean (geometric coefficient of variation)	31.4 (± 54)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Serum Onartuzumab Concentration (Cmax)

End point title	Maximum Observed Serum Onartuzumab Concentration (Cmax) ^[18]
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End point description:

Safety population. Here, "Number of subjects analysed" indicates the total number of participants who provided evaluable data for this endpoint.

End point type	Secondary
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End point timeframe:

30 minutes after end of infusion (duration of infusion = 60 minutes) on Cycle 1 Day 1 (cycle length = 14 days)

Notes:

[18] - 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: Only participants who received onartuzumab were included in analysis; hence only Onartuzumab + mFOLFOX6 arm is reported.

End point values	Onartuzumab + mFOLFOX6			
Subject group type	Reporting group			
Number of subjects analysed	203			
Units: mcg/mL				
geometric mean (geometric coefficient of variation)	242 (± 31)			

Statistical analyses

No statistical analyses for this end point

Secondary: European Organization for Research and Treatment Cancer Quality of Life Questionnaire (EORTC QLQ) Core 30 (EORTC QLQ-C30) Version 3 Score

End point title	European Organization for Research and Treatment Cancer Quality of Life Questionnaire (EORTC QLQ) Core 30 (EORTC QLQ-C30) Version 3 Score
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End point description:

EORTC QLQ-C30: included functional scales (physical, role, cognitive, emotional, and social), global health status, symptom scales (fatigue, pain, nausea/vomiting) and single items (dyspnoea, appetite loss, insomnia, constipation/diarrhea and financial difficulties). Most questions used 4 point scale (1 'Not at all' to 4 'Very much'; 2 questions used 7-point scale (1 'very poor' to 7 'Excellent'). Scores averaged, transformed to 0-100 scale; higher score=better level of functioning or greater degree of symptoms. As per protocol, the secondary efficacy endpoints (including patient-reported endpoints) were only to be analyzed if the primary outcome results in statistical significance. As the pre-specified criterion was not met, the analysis was not performed.

End point type	Secondary
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End point timeframe:

Day 1 of each treatment Cycle up to end of treatment (EOT) (up to approximately 1.5 years) (1 Cycle= 21 days)

End point values	Placebo + mFOLFOX6	Onartuzumab + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[19]	0 ^[20]		
Units: Units on scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[19] - As the pre-specified criteria was not met, the analysis was not performed.

[20] - As the pre-specified criteria was not met, the analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: EORTC QLQ-Gastric cancer Specific Quality of Life Questionnaire (EORTC QLQ-STOC22) Score

End point title	EORTC QLQ-Gastric cancer Specific Quality of Life Questionnaire (EORTC QLQ-STOC22) Score
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End point description:

EORTC QLQ-STOC22: included symptom or problem scale (eating problems, discomfort, pain, bloating, indigestion, nausea/vomiting, dry mouth). Questions used 4 point scale (1 'Not at all' to 4 'Very much'; higher score=better level of functioning or greater degree of symptoms. As per protocol, the secondary efficacy endpoints (including patient-reported endpoints) were only to be analyzed if the primary outcome results in statistical significance. As the pre-specified criterion was not met, the analysis was not performed.

End point type	Secondary
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End point timeframe:

Day 1 of each treatment Cycle up to EOT (up to approximately 1.5 years) (1 Cycle= 21 days)

End point values	Placebo + mFOLFOX6	Onartuzumab + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[21]	0 ^[22]		
Units: Units on scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[21] - As the pre-specified criteria was not met, the analysis was not performed.

[22] - As the pre-specified criteria was not met, the analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: European Quality of Life-5 Dimensions (EQ-5D) Questionnaire Score

End point title	European Quality of Life-5 Dimensions (EQ-5D) Questionnaire Score
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End point description:

EQ-5D: participant rated questionnaire to assess health-related quality of life in terms of a single utility score. Health State Profile component assesses level of current health for 5 domains: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression; 1 indicates better health state (no problems); 3 indicates worst health state ("confined to bed"). Scoring formula developed by EuroQol Group assigns a utility value for each domain in the profile. Score is transformed and results in a total score range -0.594 to 1.000; higher score indicates a better health state. As per protocol, the secondary efficacy endpoints (including patient-reported endpoints) were only to be analyzed if the primary outcome results in statistical significance. As the pre-specified criterion was not met, the analysis was not performed.

End point type	Secondary
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End point timeframe:

Day 1 of each treatment Cycle up to EOT (up to approximately 1.5 years) (1 Cycle= 21 days)

End point values	Placebo + mFOLFOX6	Onartuzumab + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[23]	0 ^[24]		
Units: Units on scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[23] - As the pre-specified criteria was not met, the analysis was not performed.

[24] - As the pre-specified criteria was not met, the analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) as Determined by Investigator Using RECIST v1.1: Met 2 + /3 + Subgroup GEC Participants

End point title	Duration of Response (DOR) as Determined by Investigator Using RECIST v1.1: Met 2 + /3 + Subgroup GEC Participants
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End point description:

DOR is defined as the duration from the first tumor assessment that supports the participant's objective response (CR or PR, whichever is first recorded) to PD or death due to any cause, whichever occurs first. Participants who are alive and have not experienced PD at the time of analysis were censored at the time of the last tumor assessment. Participants with no post-baseline tumor assessment were censored at the randomization date plus 1 day. PD: at least 20% increase in the sum of diameters of target lesions compared to the smallest sum of diameters on-study and absolute increase of at least 5 mm, progression of existing non-target lesions, or presence of new lesions. DOR was estimated using Kaplan-Meier methodology. As per protocol, the secondary efficacy endpoints (including patient-reported endpoints) were only to be analyzed if the primary outcome results in statistical significance. As the pre-specified criterion was not met, the analysis was not performed.

End point type	Secondary
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End point timeframe:

Baseline up to disease progression or death due to any cause, whichever occurred first (up to approximately 1.5 years)

End point values	Placebo + mFOLFOX6	Onartuzumab + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[25]	0 ^[26]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[25] - As the pre-specified criteria was not met, the analysis was not performed.

[26] - As the pre-specified criteria was not met, the analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: DOR as Determined by Investigator Using RECIST v1.1: ITT Population

End point title	DOR as Determined by Investigator Using RECIST v1.1: ITT Population
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End point description:

DOR is defined as the duration from the first tumor assessment that supports the participant's objective response (CR or PR, whichever is first recorded) to PD or death due to any cause, whichever occurs first.

Participants who are alive and have not experienced PD at the time of analysis were censored at the time of the last tumor assessment. Participants with no post-baseline tumor assessment were censored at the randomization date plus 1 day. PD: at least 20% increase in the sum of diameters of target lesions compared to the smallest sum of diameters on-study and absolute increase of at least 5 mm, progression of existing non-target lesions, or presence of new lesions. DOR was estimated using Kaplan-Meier methodology. As per protocol, the secondary efficacy endpoints (including patient-reported endpoints) were only to be analyzed if the primary outcome results in statistical significance. As the pre-specified criterion was not met, the analysis was not performed.

End point type	Secondary
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End point timeframe:

Baseline up to disease progression or death due to any cause, whichever occurred first (up to approximately 3 years)

End point values	Placebo + mFOLFOX6	Onartuzumab + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[27]	0 ^[28]		
Units: Units on scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[27] - As the pre-specified criteria was not met, the analysis was not performed.

[28] - As the pre-specified criteria was not met, the analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in ATAs Level of Onartuzumab

End point title	Change from Baseline in ATAs Level of Onartuzumab
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End point description:

Safety population. As per protocol, the secondary efficacy endpoints (including patient-reported endpoints) were only to be analyzed if the primary outcome results in statistical significance. As the pre-specified criteria was not met, the analysis was not performed.

End point type	Secondary
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End point timeframe:

Baseline (pre-dose [within 1 hour before infusion start] on Cycle 1 Day 1), pre-dose on Cycle 4 Day 1 (cycle length = 14 days), at study drug discontinuation visit (up to 3 years)

End point values	Placebo + mFOLFOX6	Onartuzumab + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[29]	0 ^[30]		
Units: Titer unit				
arithmetic mean (standard deviation)	()	()		

Notes:

[29] - As the pre-specified criteria was not met, the analysis was not performed.

[30] - As the pre-specified criteria was not met, the analysis was not performed.

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 30 days after the last administration of study drug (approximately up to 3 years)

Adverse event reporting additional description:

Safety population

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	Placebo + mFOLFOX6
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Reporting group description:

Placebo matched to onartuzumab was administered by IV infusion (first infusion for 60 minutes, and subsequently for 30 minutes) on Day 1 of each 14-day cycle followed by mFOLFOX6 regimen comprising of oxaliplatin 85 mg/m² IV, folinic acid (400 mg/m²) or levofolinic acid (200 mg/m²) or as deemed appropriate per investigator and 5-FU 400 mg/m² IV bolus, then 5-FU 2400 mg/m² continuous IV infusion over 46 to 48 hours until 12 cycles. Participants without disease progression after 12 cycles of mFOLFOX6 with placebo, further continued treatment with placebo until disease progression, unacceptable toxicity, or death.

Reporting group title	Onartuzumab + mFOLFOX6
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Reporting group description:

Onartuzumab 10 mg/kg in 250 mL final 0.9% NSS was administered by IV infusion (first infusion for 60 minutes, and subsequently for 30 minutes) on Day 1 of each 14-day cycle followed by mFOLFOX6 regimen comprising of oxaliplatin 85 mg/m² IV, folinic acid (400 mg/m²) or levofolinic acid (200 mg/m²) or as deemed appropriate per investigator and 5-FU 400 mg/m² IV bolus, then 5-FU 2400 mg/m² continuous IV infusion over 46 to 48 hours until 12 cycles. Participants without disease progression after 12 cycles of mFOLFOX6 with onartuzumab, further continued treatment with onartuzumab until disease progression, unacceptable toxicity, or death.

Serious adverse events	Placebo + mFOLFOX6	Onartuzumab + mFOLFOX6	
Total subjects affected by serious adverse events			
subjects affected / exposed	95 / 280 (33.93%)	111 / 279 (39.78%)	
number of deaths (all causes)	160	164	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pericardial effusion malignant			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour necrosis			

subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tumour pain			
subjects affected / exposed	1 / 280 (0.36%)	2 / 279 (0.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour perforation			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Axillary vein thrombosis			
subjects affected / exposed	0 / 280 (0.00%)	2 / 279 (0.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 280 (0.36%)	6 / 279 (2.15%)	
occurrences causally related to treatment / all	1 / 1	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	0 / 280 (0.00%)	2 / 279 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein thrombosis			

subjects affected / exposed	0 / 280 (0.00%)	2 / 279 (0.72%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	0 / 280 (0.00%)	2 / 279 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 280 (0.36%)	2 / 279 (0.72%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Device dislocation			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion			

subjects affected / exposed	2 / 280 (0.71%)	3 / 279 (1.08%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 280 (0.00%)	2 / 279 (0.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Generalised oedema			
subjects affected / exposed	0 / 280 (0.00%)	3 / 279 (1.08%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 280 (0.36%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device pain			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 280 (0.00%)	3 / 279 (1.08%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			

subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (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	6 / 280 (2.14%)	3 / 279 (1.08%)	
occurrences causally related to treatment / all	1 / 7	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	2 / 280 (0.71%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Aspiration			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dysaesthesia pharynx			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 280 (0.36%)	2 / 279 (0.72%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea at rest			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pleural effusion			
subjects affected / exposed	0 / 280 (0.00%)	2 / 279 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonitis			
subjects affected / exposed	0 / 280 (0.00%)	2 / 279 (0.72%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	4 / 280 (1.43%)	7 / 279 (2.51%)	
occurrences causally related to treatment / all	3 / 4	4 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Weight decreased			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Arterial restenosis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal anastomotic leak			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Laceration			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin injury			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	2 / 280 (0.71%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	

Subdural haemorrhage			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular access complication			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Pyloric stenosis			
subjects affected / exposed	3 / 280 (1.07%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial thrombosis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	

Cardiac failure			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction			
subjects affected / exposed	1 / 280 (0.36%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	0 / 280 (0.00%)	2 / 279 (0.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 2	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Nervous system disorder			

subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	2 / 280 (0.71%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior sagittal sinus thrombosis			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (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			
Anaemia			
subjects affected / exposed	4 / 280 (1.43%)	5 / 279 (1.79%)	
occurrences causally related to treatment / all	4 / 5	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	5 / 280 (1.79%)	5 / 279 (1.79%)	
occurrences causally related to treatment / all	4 / 5	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	5 / 280 (1.79%)	6 / 279 (2.15%)	
occurrences causally related to treatment / all	5 / 5	9 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			

subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
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 / 280 (0.36%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	2 / 280 (0.71%)	2 / 279 (0.72%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	2 / 280 (0.71%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 280 (0.00%)	2 / 279 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	2 / 280 (0.71%)	8 / 279 (2.87%)	
occurrences causally related to treatment / all	2 / 2	6 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			
subjects affected / exposed	0 / 280 (0.00%)	2 / 279 (0.72%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric stenosis			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal perforation			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal toxicity			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (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	0 / 280 (0.00%)	2 / 279 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 280 (0.36%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intestinal perforation			

subjects affected / exposed	2 / 280 (0.71%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	4 / 280 (1.43%)	2 / 279 (0.72%)	
occurrences causally related to treatment / all	2 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			
subjects affected / exposed	2 / 280 (0.71%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal obstruction			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal haemorrhage			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
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	2 / 280 (0.71%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 280 (0.36%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 280 (0.36%)	2 / 279 (0.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	10 / 280 (3.57%)	5 / 279 (1.79%)	
occurrences causally related to treatment / all	7 / 11	4 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Jaundice cholestatic			

subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
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			
Erythema ab igne			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 280 (0.36%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			

subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (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			
Bronchitis			
subjects affected / exposed	1 / 280 (0.36%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
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	1 / 280 (0.36%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diverticulitis			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastroenteritis			
subjects affected / exposed	1 / 280 (0.36%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	2 / 280 (0.71%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Laryngitis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Orchitis			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	0 / 280 (0.00%)	2 / 279 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	2 / 280 (0.71%)	7 / 279 (2.51%)	
occurrences causally related to treatment / all	2 / 2	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pyelonephritis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal abscess			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 280 (0.36%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 280 (0.36%)	2 / 279 (0.72%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 1	
Upper respiratory tract infection			
subjects affected / exposed	1 / 280 (0.36%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 280 (1.07%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			

subjects affected / exposed	2 / 280 (0.71%)	2 / 279 (0.72%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Fluid retention			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypernatraemia			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 280 (0.71%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 280 (0.36%)	2 / 279 (0.72%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			

subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	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	Placebo + mFOLFOX6	Onartuzumab + mFOLFOX6	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	257 / 280 (91.79%)	265 / 279 (94.98%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	19 / 280 (6.79%)	26 / 279 (9.32%)	
occurrences (all)	19	29	
Aspartate aminotransferase increased			
subjects affected / exposed	16 / 280 (5.71%)	26 / 279 (9.32%)	
occurrences (all)	16	28	
Weight decreased			
subjects affected / exposed	24 / 280 (8.57%)	13 / 279 (4.66%)	
occurrences (all)	25	14	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	4 / 280 (1.43%)	15 / 279 (5.38%)	
occurrences (all)	4	16	
Hypotension			
subjects affected / exposed	9 / 280 (3.21%)	17 / 279 (6.09%)	
occurrences (all)	10	18	
Nervous system disorders			
Dizziness			
subjects affected / exposed	13 / 280 (4.64%)	23 / 279 (8.24%)	
occurrences (all)	16	27	
Dysgeusia			
subjects affected / exposed	34 / 280 (12.14%)	36 / 279 (12.90%)	
occurrences (all)	39	37	
Neuropathy peripheral			

subjects affected / exposed	55 / 280 (19.64%)	59 / 279 (21.15%)	
occurrences (all)	86	89	
Neurotoxicity			
subjects affected / exposed	17 / 280 (6.07%)	11 / 279 (3.94%)	
occurrences (all)	40	17	
Paraesthesia			
subjects affected / exposed	50 / 280 (17.86%)	42 / 279 (15.05%)	
occurrences (all)	60	58	
Peripheral sensory neuropathy			
subjects affected / exposed	32 / 280 (11.43%)	19 / 279 (6.81%)	
occurrences (all)	35	20	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	47 / 280 (16.79%)	46 / 279 (16.49%)	
occurrences (all)	61	57	
Neutropenia			
subjects affected / exposed	117 / 280 (41.79%)	129 / 279 (46.24%)	
occurrences (all)	212	235	
Thrombocytopenia			
subjects affected / exposed	33 / 280 (11.79%)	52 / 279 (18.64%)	
occurrences (all)	41	68	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	54 / 280 (19.29%)	54 / 279 (19.35%)	
occurrences (all)	85	89	
Fatigue			
subjects affected / exposed	88 / 280 (31.43%)	81 / 279 (29.03%)	
occurrences (all)	138	124	
Mucosal inflammation			
subjects affected / exposed	24 / 280 (8.57%)	28 / 279 (10.04%)	
occurrences (all)	35	35	
Oedema peripheral			
subjects affected / exposed	23 / 280 (8.21%)	118 / 279 (42.29%)	
occurrences (all)	24	151	
Pyrexia			

subjects affected / exposed occurrences (all)	32 / 280 (11.43%) 37	26 / 279 (9.32%) 33	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	44 / 280 (15.71%)	38 / 279 (13.62%)	
occurrences (all)	54	51	
Abdominal pain upper			
subjects affected / exposed	22 / 280 (7.86%)	20 / 279 (7.17%)	
occurrences (all)	27	21	
Constipation			
subjects affected / exposed	63 / 280 (22.50%)	48 / 279 (17.20%)	
occurrences (all)	76	59	
Diarrhoea			
subjects affected / exposed	79 / 280 (28.21%)	84 / 279 (30.11%)	
occurrences (all)	146	136	
Dry mouth			
subjects affected / exposed	14 / 280 (5.00%)	6 / 279 (2.15%)	
occurrences (all)	16	6	
Dyspepsia			
subjects affected / exposed	24 / 280 (8.57%)	15 / 279 (5.38%)	
occurrences (all)	29	16	
Nausea			
subjects affected / exposed	141 / 280 (50.36%)	134 / 279 (48.03%)	
occurrences (all)	325	286	
Stomatitis			
subjects affected / exposed	38 / 280 (13.57%)	37 / 279 (13.26%)	
occurrences (all)	49	48	
Vomiting			
subjects affected / exposed	73 / 280 (26.07%)	68 / 279 (24.37%)	
occurrences (all)	158	124	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	26 / 280 (9.29%)	23 / 279 (8.24%)	
occurrences (all)	31	27	
Dyspnoea			

subjects affected / exposed	26 / 280 (9.29%)	23 / 279 (8.24%)	
occurrences (all)	29	25	
Epistaxis			
subjects affected / exposed	14 / 280 (5.00%)	11 / 279 (3.94%)	
occurrences (all)	17	12	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	43 / 280 (15.36%)	34 / 279 (12.19%)	
occurrences (all)	46	37	
Rash			
subjects affected / exposed	11 / 280 (3.93%)	20 / 279 (7.17%)	
occurrences (all)	13	23	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	30 / 280 (10.71%)	14 / 279 (5.02%)	
occurrences (all)	36	14	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	15 / 280 (5.36%)	19 / 279 (6.81%)	
occurrences (all)	16	21	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	76 / 280 (27.14%)	76 / 279 (27.24%)	
occurrences (all)	122	115	
Hypoalbuminaemia			
subjects affected / exposed	10 / 280 (3.57%)	61 / 279 (21.86%)	
occurrences (all)	14	76	
Hypocalcaemia			
subjects affected / exposed	0 / 280 (0.00%)	18 / 279 (6.45%)	
occurrences (all)	0	20	
Hypokalaemia			
subjects affected / exposed	18 / 280 (6.43%)	24 / 279 (8.60%)	
occurrences (all)	26	29	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 September 2012	<ul style="list-style-type: none">- Met IHC stratification factor (formerly a clinical score of 1+ vs. 2+/3+ based on a $\geq 50\%$ analytical cutoff) and primary tumor location has been replaced with 5 stratification levels encompassing a $\geq 50\%$ and $\geq 90\%$ analytical cutoff (I, II, III, IV, and V).- Baseline weight (rather than screening weight) was used to calculate onartuzumab/placebo dosage.- The exclusion criterion regarding history of malignancy has been modified, and exclusion criterion regarding known sensitivity to components of study treatment has been updated to include known contraindications.- Procedures for potential emergency unblinding have been revised.- Live vaccines have been added to the list of prohibited concomitant medications.- Text has been added to indicate that participants must receive the first dose of study drug within 3 days after randomization.- Description of the tumor assessment schedule and text concerning chemotherapy dose modification has been updated.- The protocol has been amended to specify pharmacokinetics (PK)/ATA evaluation at selected centers only.- Text has been added to indicate that objective response rate has been evaluated in all randomized participants.- The rationale for the study design has been updated.

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.

As per protocol, the secondary efficacy outcomes (including patient-reported outcomes) were only to be analyzed if the primary outcome results in statistical significance. As the pre-specified criteria was not met, the analysis was not performed.

Notes: