

**Clinical trial results:**

A perioperative, single-arm multicenter Phase II academic trial to investigate the efficacy and safety of panitumumab in combination with irinotecan/5-fluorouracil/leucovorin (FOLFIRI) in patients with previously untreated, wild-type RAS, potentially resectable colorectal cancer liver metastases

Summary

EudraCT number	2012-000265-20
Trial protocol	AT
Global end of trial date	15 May 2020

Results information

Result version number	v2 (current)
This version publication date	30 September 2023
First version publication date	21 October 2021
Version creation reason	<ul style="list-style-type: none">• New data added to full data set Inclusion of follow-up data endpoints; update secondary endpoints, timepoint of analysis and adverse events

Trial information**Trial identification**

Sponsor protocol code	LM02
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Amgen Identifier: ISS 20109160

Notes:

Sponsors

Sponsor organisation name	ABCSG (Austrian Breast & Colorectal Cancer Study Group)
Sponsor organisation address	Nußdorfer Platz 8/12, Vienna, Austria, 1190
Public contact	Trial Office, ABCSG (Austrian Breast & Colorectal Cancer Study Group), +43 14089230, info@abcsbg.at
Scientific contact	Prof. Josef Thaler (Coordinating Investigator), ABCSG (Austrian Breast & Colorectal Cancer Study Group), +43 14089230, info@abcsbg.at

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 May 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	15 May 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of perioperative treatment including panitumumab and FOLFIRI as first line therapy for mCRC in subjects with potentially resectable liver metastases expressing wild-type RAS

Protection of trial subjects:

The study specific patient information and informed consent form included language to encourage study participants to reach out to the Study Doctor / Study Team in case they have any questions, concerns or doubts. Section 14 specifically referenced a 24/7 contact person to reach out to and the ICF contained a reference to the local ombudsman / patient advocacy. A dedicated DMC was established to ensure patient safety throughout the trial and any safety requests could be addressed to the DMC members for their expertise and input, always considering patient safety and well-being in their decisions.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 October 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 36
Worldwide total number of subjects	36
EEA total number of subjects	36

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	16
From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Single-arm study with patient registration where study sites provided registration form to ABCSG via fax and a study specific identifier was assigned by ABCSG and returned to study sites in completed form.

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	36
Number of subjects completed	36

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Panitumumab + FOLFIRI
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Arm description:

Panitumumab in combination with irinotecan/5-fluorouracil/leucovorin (FOLFIRI)

Arm type	Experimental
Investigational medicinal product name	Panitumumab (Vectibix®) (IMP)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

6 mg/kg; totally 24 weeks before and after the surgery

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

Dosage and administration details:

180 mg/m²; 4 cycles (neoadjuvant) and 8 cycles (adjuvant) (1 cycle=2 weeks)

Investigational medicinal product name	5-fluorouracil (NIMP)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

daily 2800 mg/ml (1x 400 (d1; iv bolus) followed by 2400 (over 46 hours iv infusion every 2 weeks); 4 cycles (neoadjuvant) and 8 cycles (adjuvant) (1 cycle = 2 weeks)

Investigational medicinal product name	Folinic acid (Leucovorin) (NIMP)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solvent for parenteral use

Routes of administration	Intravenous use
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Dosage and administration details:

400 mg/m²; 4 cycles (neoadjuvant) and 8 cycles (adjuvant) (1 cycle = 2 weeks)

Number of subjects in period 1	Panitumumab + FOLFIRI
Started	36
Completed	20
Not completed	16
Adverse event, serious fatal	3
Death from other reason	2
Consent withdrawn by subject	5
Death from primary carcinoma	5
Missing informed consent	1

Baseline characteristics

Reporting groups

Reporting group title	Panitumumab + FOLFIRI
Reporting group description:	
Panitumumab in combination with irinotecan/5-fluorouracil/leucovorin (FOLFIRI)	

Reporting group values	Panitumumab + FOLFIRI	Total	
Number of subjects	36	36	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	16	16	
From 65-84 years	20	20	
85 years and over	0	0	
Age continuous			
Units: years			
median	66		
full range (min-max)	32 to 81	-	
Gender categorical			
Units: Subjects			
Female	7	7	
Male	28	28	
Missing	1	1	
ECOG Performance Status			
Units: Subjects			
'0'	29	29	
'1'	6	6	
Missing	1	1	
T-stage			
Units: Subjects			
T1	1	1	
T2	5	5	
T3	21	21	
TX	6	6	
Missing	3	3	
N-stage			
Units: Subjects			
N0	11	11	
N1	8	8	
N2	5	5	
NX	8	8	

Missing	4	4	
Primary tumor location			
Units: Subjects			
Colon	19	19	
Rectum	10	10	
Rectum and Colon	5	5	
Other	1	1	
Missing	1	1	
Prior chemotherapy			
Units: Subjects			
yes	7	7	
no	28	28	
Missing	1	1	

Subject analysis sets

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All enrolled patients with signed informed consent.	

Reporting group values	ITT		
Number of subjects	35		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	16		
From 65-84 years	19		
85 years and over	0		
Age continuous			
Units: years			
median	66		
full range (min-max)	32 to 81		
Gender categorical			
Units: Subjects			
Female	7		
Male	28		
Missing	0		
ECOG Performance Status			
Units: Subjects			
'0'	29		
'1'	6		
Missing	0		
T-stage			
Units: Subjects			

T1	1		
T2	5		
T3	21		
TX	6		
Missing	2		
N-stage			
Units: Subjects			
N0	11		
N1	8		
N2	5		
NX	8		
Missing	3		
Primary tumor location			
Units: Subjects			
Colon	19		
Rectum	10		
Rectum and Colon	5		
Other	1		
Missing	0		
Prior chemotherapy			
Units: Subjects			
yes	7		
no	28		
Missing	0		

End points

End points reporting groups

Reporting group title	Panitumumab + FOLFIRI
Reporting group description: Panitumumab in combination with irinotecan/5-fluorouracil/leucovorin (FOLFIRI)	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: All enrolled patients with signed informed consent.	

Primary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR) ^[1]
End point description: Objective response rate (ORR) is evaluated using RECIST (1.1), measured by multislice 3-phase CT and is based on target and non-target lesions. Missing radiological response evaluation is evaluated as no objective response. ORR is defined as the proportion of patients with overall response of CR (complete response) or PR (partial response). The number of patients with objective response, as well as the estimated rate and the exact 95% confidence intervals are given.	
End point type	Primary
End point timeframe: After neoadjuvant therapy (4 cycles)	

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: It is not possible in EudraCT to enter statistical analysis for single-arm studies - the estimated rate with the 95% confidence interval was therefore included in the description.

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	35 ^[2]			
Units: Subjects				
yes	23			
no	12			

Notes:

[2] - The estimated ORR is 0.66 with a two-sided 95% confidence interval (CI) of [0.48, 0.81].

Statistical analyses

No statistical analyses for this end point

Primary: Diarrhoea Grade 3/4

End point title	Diarrhoea Grade 3/4 ^[3]
End point description: The safety primary endpoint is to assess the rate of patients with at least one diarrhoea event of grade 3 or 4 (Common Terminology Criteria for Adverse Events (CTCAE) v4.0). For patients without early end of therapy/study before neoadjuvant staging: if diarrhoea documentation for a neoadjuvant therapy visit is missing and there is no prior documented diarrhoea grade III/IV adverse event -- no diarrhoea grade III/IV is assumed for that cycle. For patients with early end of treatment/study before neoadjuvant staging visit: o no diarrhoea Grade III/IV is assumed if the patient died without disease o a diarrhoea Grade III/IV is assumed if the patient had an early end of therapy due to disease progression, due to other (no diarrhoea) toxicity or if the patient withdraws Informed consent during neoadjuvant therapy	

The number of patients with Diarrhoea Grade 3/4 is given.

End point type	Primary
End point timeframe:	
During 4 cycles of neoadjuvant therapy	
Notes:	
[3] - 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: Analysis is descriptive only.	

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	35			
Units: Subjects				
yes	5			
no	30			

Statistical analyses

No statistical analyses for this end point

Secondary: ORR in patients without liver tissue damage

End point title	ORR in patients without liver tissue damage
End point description:	
Objective response rate (ORR) is evaluated using RECIST (1.1), measured by multislice 3-phase CT and is based on target and non-target lesions. Missing radiological response evaluation is evaluated as no objective response. ORR is defined as the proportion of patients with overall response of CR (complete response) or PR (partial response). The number of patients with objective response in those without liver tissue damage, as well as the number of patients with liver tissue damage are given. Presence of liver tissue damage is defined as chemotherapy-associated steatohepatitis (CASH) or chemotherapy-associated liver injuries. CASH is evaluated through NAFLD activity score (NAS) and Fibrosis score. A NAS score of greater or equal to 3 with or without any fibrosis are diagnostic for CASH. Liver injuries are defined as presence of CASH, sinusoidal obstruction syndrome (SOS) or nodular regenerative hyperplasia (NRH). No liver tissue damage is assumed if neither CASH nor SOS nor NRH occurs.	
End point type	Secondary
End point timeframe:	
After neoadjuvant therapy (4 cycles)	

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	5 ^[4]			
Units: Subjects				
yes	5			
no	0			

Notes:

[4] - 5 patients didn't have liver damage (CASH), 13 patients had; 17 had missing documentation

Statistical analyses

No statistical analyses for this end point

Secondary: Resection rate

End point title	Resection rate
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End point description:

All liver lesions resected after final liver metastases surgery are evaluated. Liver lesions with resection margin status R2 (macroscopic residual tumor) are not considered as resected, while RX/R0/R1 are considered as resected. The liver resection rate is evaluated through the number of patients with documented surgery of liver metastases and with all liver lesions resected after final liver metastases surgery. The number of patients with liver resection, as well as the estimated rate and the exact 95% confidence intervals are given.

End point type	Secondary
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End point timeframe:

After neoadjuvant chemotherapy

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	35 ^[5]			
Units: Subjects				
yes	29			
no	6			

Notes:

[5] - The estimated resection rate is 0.83 with a two-sided 95% confidence interval (CI) of [0.66, 0.93].

Statistical analyses

No statistical analyses for this end point

Secondary: Perioperative morbidity and mortality

End point title	Perioperative morbidity and mortality
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End point description:

Perioperative morbidity is measured by Dindo classification during post-operative stay. Perioperative mortality is defined as any death, regardless of cause, occurring within 30 days after surgery. The number of patients with perioperative morbidity and mortality is given in the different grade categories.

End point type	Secondary
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End point timeframe:

During post-operative stay

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	28 ^[6]			
Units: Subjects				
Grade I	22			
Grade II	3			
Grade IIIb	1			

Grade IVa	1			
Grade V	1			

Notes:

[6] - From 29 patients with surgery of liver metastases, classification was documented for 28 patients.

Statistical analyses

No statistical analyses for this end point

Secondary: Complete pathological response

End point title	Complete pathological response
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End point description:

Pathological response of neoadjuvant chemotherapy is measured by tumor regression grade, a histological tumor response assessment of hepatic colorectal metastases established by Rubbia-Brandt et al. Complete pathological response is defined as a tumor with Rubbia-Brandt tumor regression grade (TRG) 1. The number of patients with complete pathological response is reported.

End point type	Secondary
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End point timeframe:

At surgery

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	25 ^[7]			
Units: Subjects				
yes	2			
no	23			

Notes:

[7] - For 25 of the 29 patients who underwent surgery of liver metastases TRG was evaluable.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)
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End point description:

Progression-free survival (PFS) was defined as the time from registration date to the date of first observed progression (defined as occurrence of new secondary carcinoma or death of any cause whichever comes first). Patients who had no progression and did not die prior to the analysis data cut-off date were censored at their last known progression free date. Survival rate estimates at 24 months with 2-sided 95% confidence intervals were calculated by Kaplan-Meier method.

End point type	Secondary
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End point timeframe:

end of study

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	35			
Units: percent				
number (confidence interval 95%)	30.8 (16.2 to 46.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)
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End point description:

Overall survival (OS) was defined as the time from registration date to the date of death (of any cause). Patients who did not die prior to the analysis data cut-off date were censored at their last contact date. Survival rate estimates at 24 months with 2-sided 95% confidence intervals were calculated by Kaplan-Meier method.

End point type	Secondary
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End point timeframe:

end of study

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	35			
Units: percent				
number (confidence interval 95%)	73.3 (54.8 to 85.1)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

(S)AE reporting was mandatory from the date of informed consent form signature (i.e., screening phase) until 42 days after the last dose of neoadjuvant study treatment.

Adverse event reporting additional description:

Screening Phase: only AEs deemed to be serious (SAEs) and related to protocol mandated and not routinely performed procedures have to be reported.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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Reporting groups

Reporting group title	Pertuzumab+Trastuzumab+Epirubicin (Arm B)
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Reporting group description: -

Reporting group title	Atezolizumab+Pertuzumab+Trastuzumab+Epirubicin (Arm A)
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Reporting group description: -

Serious adverse events	Pertuzumab+Trastuzumab+Epirubicin (Arm B)	Atezolizumab+Pertuzumab+Trastuzumab+Epirubicin (Arm A)	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 29 (20.69%)	5 / 29 (17.24%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Infusion related reaction	Additional description: Infusion related reaction		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 29 (10.34%)	3 / 29 (10.34%)	
occurrences causally related to treatment / all	3 / 3	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiomyopathy	Additional description: Cardiomyopathy		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (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			
Febrile neutropenia	Additional description: Febrile neutropenia		

alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 29 (3.45%)	2 / 29 (6.90%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration	Additional description: General physical health deterioration		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Alveolar osteitis	Additional description: Alveolar osteitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19	Additional description: COVID-19		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection	Additional description: Febrile infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Pertuzumab+Trastuzumab+Epirubicin (Arm B)	Atezolizumab+Pertuzumab+Trastuzumab+Epirubicin (Arm A)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 29 (100.00%)	29 / 29 (100.00%)	

Vascular disorders			
Hypotension	Additional description: Hypotension		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 29 (3.45%)	2 / 29 (6.90%)	
occurrences (all)	1	2	
Hot flush	Additional description: Hot flush		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 29 (6.90%)	3 / 29 (10.34%)	
occurrences (all)	2	3	
Hypertension	Additional description: Hypertension		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 29 (6.90%)	2 / 29 (6.90%)	
occurrences (all)	2	2	
Thrombophlebitis	Additional description: Thrombophlebitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 29 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Fatigue	Additional description: Fatigue		
alternative assessment type: Non-systematic			
subjects affected / exposed	17 / 29 (58.62%)	14 / 29 (48.28%)	
occurrences (all)	35	29	
Chills	Additional description: Chills		
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 29 (24.14%)	7 / 29 (24.14%)	
occurrences (all)	7	8	
Pyrexia	Additional description: Pyrexia		
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 29 (24.14%)	5 / 29 (17.24%)	
occurrences (all)	8	8	
Pain	Additional description: Pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 29 (3.45%)	2 / 29 (6.90%)	
occurrences (all)	1	2	
Mucosal inflammation	Additional description: Mucosal inflammation		

alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	5 / 29 (17.24%) 6	5 / 29 (17.24%) 8	
Influenza like illness	Additional description: Influenza like illness		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	2 / 29 (6.90%) 2	
Reproductive system and breast disorders			
Breast pain	Additional description: Breast pain		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1	2 / 29 (6.90%) 2	
Vulvovaginal dryness	Additional description: Vulvovaginal dryness		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	2 / 29 (6.90%) 2	
Respiratory, thoracic and mediastinal disorders			
Cough	Additional description: Cough		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1	2 / 29 (6.90%) 4	
Dyspnoea exertional	Additional description: Dyspnoea exertional		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2	0 / 29 (0.00%) 0	
Epistaxis	Additional description: Epistaxis		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2	2 / 29 (6.90%) 2	
Nasal dryness	Additional description: Nasal dryness		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	4 / 29 (13.79%) 4	1 / 29 (3.45%) 1	
Rhinorrhoea	Additional description: Rhinorrhoea		

alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1	2 / 29 (6.90%) 2	
Psychiatric disorders			
Sleep disorder	Additional description: Sleep disorder		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	3 / 29 (10.34%) 3	
Injury, poisoning and procedural complications			
Infusion related reaction	Additional description: Infusion related reaction		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	3 / 29 (10.34%) 3	2 / 29 (6.90%) 2	
Nervous system disorders			
Dysgeusia	Additional description: Dysgeusia		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1	3 / 29 (10.34%) 4	
Ageusia	Additional description: Ageusia		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2	0 / 29 (0.00%) 0	
Headache	Additional description: Headache		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	8 / 29 (27.59%) 16	7 / 29 (24.14%) 7	
Paraesthesia	Additional description: Paraesthesia		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2	3 / 29 (10.34%) 4	
Polyneuropathy	Additional description: Polyneuropathy		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2	3 / 29 (10.34%) 5	
Taste disorder	Additional description: Taste disorder		

alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	3 / 29 (10.34%) 5	2 / 29 (6.90%) 3	
Blood and lymphatic system disorders			
Neutropenia	Additional description: Neutropenia		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	4 / 29 (13.79%) 7	6 / 29 (20.69%) 9	
Leukopenia	Additional description: Leukopenia		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1	3 / 29 (10.34%) 3	
Anaemia	Additional description: Anaemia		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	3 / 29 (10.34%) 4	3 / 29 (10.34%) 6	
Ear and labyrinth disorders			
Vertigo	Additional description: Vertigo		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 4	3 / 29 (10.34%) 10	
Eye disorders			
Visual impairment	Additional description: Visual impairment		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2	2 / 29 (6.90%) 2	
Dry eye	Additional description: Dry eye		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	3 / 29 (10.34%) 4	1 / 29 (3.45%) 1	
Gastrointestinal disorders			
Nausea	Additional description: Nausea		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	20 / 29 (68.97%) 45	20 / 29 (68.97%) 38	
Diarrhoea	Additional description: Diarrhoea		

alternative assessment type: Non-systematic			
subjects affected / exposed	18 / 29 (62.07%)	17 / 29 (58.62%)	
occurrences (all)	43	42	
Constipation	Additional description: Constipation		
alternative assessment type: Non-systematic			
subjects affected / exposed	8 / 29 (27.59%)	5 / 29 (17.24%)	
occurrences (all)	15	9	
Abnormal faeces	Additional description: Abnormal faeces		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 29 (6.90%)	0 / 29 (0.00%)	
occurrences (all)	2	0	
Abdominal pain upper	Additional description: Abdominal pain upper		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 29 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Stomatitis	Additional description: Stomatitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 29 (10.34%)	2 / 29 (6.90%)	
occurrences (all)	4	2	
Vomiting	Additional description: Vomiting		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 29 (6.90%)	3 / 29 (10.34%)	
occurrences (all)	6	4	
Dyspepsia	Additional description: Dyspepsia		
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 29 (17.24%)	2 / 29 (6.90%)	
occurrences (all)	8	2	
Hepatobiliary disorders			
Hypertransaminasaemia	Additional description: Hypertransaminasaemia		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 29 (10.34%)	1 / 29 (3.45%)	
occurrences (all)	3	2	
Skin and subcutaneous tissue disorders			

Nail disorder alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Nail disorder		
	0 / 29 (0.00%)	2 / 29 (6.90%)	
	0	2	
Pruritus alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Pruritus		
	1 / 29 (3.45%)	3 / 29 (10.34%)	
	2	3	
Intertrigo alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Intertrigo		
	0 / 29 (0.00%)	2 / 29 (6.90%)	
	0	3	
Eczema alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Eczema		
	3 / 29 (10.34%)	0 / 29 (0.00%)	
	5	0	
Alopecia alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Alopecia		
	8 / 29 (27.59%)	12 / 29 (41.38%)	
	10	14	
Dry skin alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Dry skin		
	5 / 29 (17.24%)	4 / 29 (13.79%)	
	5	4	
Rash alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Rash		
	4 / 29 (13.79%)	3 / 29 (10.34%)	
	5	3	
Renal and urinary disorders			
Dysuria alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Dysuria		
	0 / 29 (0.00%)	2 / 29 (6.90%)	
	0	2	
Endocrine disorders			

Immune-mediated hyperthyroidism alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Immune-mediated hyperthyroidism		
	2 / 29 (6.90%) 2	2 / 29 (6.90%) 2	
Musculoskeletal and connective tissue disorders			
	Additional description: Arthralgia		
	2 / 29 (6.90%) 3	5 / 29 (17.24%) 5	
	Additional description: Pain in extremity		
	2 / 29 (6.90%) 3	1 / 29 (3.45%) 1	
	Additional description: Myalgia		
	2 / 29 (6.90%) 3	3 / 29 (10.34%) 3	
	Additional description: Muscle spasms		
	2 / 29 (6.90%) 2	1 / 29 (3.45%) 1	
	Additional description: Back pain		
	3 / 29 (10.34%) 3	1 / 29 (3.45%) 3	
Infections and infestations			
	Additional description: Urinary tract infection		
	1 / 29 (3.45%) 2	4 / 29 (13.79%) 7	
	Additional description: Rhinitis		
	2 / 29 (6.90%) 2	2 / 29 (6.90%) 2	
	Additional description: Respiratory tract infection		

alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 29 (6.90%)	1 / 29 (3.45%)	
occurrences (all)	2	1	
Oral herpes	Additional description: Oral herpes		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 29 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	3	
Nasopharyngitis	Additional description: Nasopharyngitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 29 (17.24%)	1 / 29 (3.45%)	
occurrences (all)	5	1	
Candida infection	Additional description: Candida infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 29 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
Decreased appetite	Additional description: Decreased appetite		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 29 (13.79%)	6 / 29 (20.69%)	
occurrences (all)	6	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 September 2013	Approval for anti-EGFR therapy with Panitumumab was adapted for patients with wild-type RAS mCRC (without mutations in exon 2,3 and 4 of KAS and NRAS) which was reflected in the amendment, along with changes and clarifications in protocol definitions, endpoints, recruitment period (extension to 24 months), as well as administrative and technical updates and corrections (e.g. change of datamanagement system, typo corrections).

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.

Limitation of a nonrandomized design.

Notes: