Clinical trial results:
A two arm phase II study of FOLFIRI in combination with standard or escalating dose of cetuximab as first line treatment of K-Ras wild type metastatic colorectal cancer: Everest 2

Summary

EudraCT number	2009-009992-36
Trial protocol	BE ES AT HU
Global end of trial date	09 July 2018

Results information

Result version number	v1 (current)
This version publication date	08 August 2019
First version publication date	08 August 2019
Summary attachment (see zip file)	Synopsis/discussion/conclusions (01 Everest 2 synopsis_discussion_conclusions.pdf) CONSORT diagram (02 Everest 2 CONSORT diagram.pdf) PFS censoring rules (03 Everest 2 PFS censoring rules.pdf) Deaths on treatment (04 Everest 2 deaths on treatment and within 30 days from last dose.pdf) Protocol deviations (05 Everest 2 protocol deviations.pdf) References (06 Everest 2 selected references.pdf) Publications (07 Everest 2 publications.pdf) Abbreviations (08 Everest 2 abbreviations.pdf)

Trial information

Trial identification

Sponsor protocol code	S51532

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01251536
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UZ Leuven
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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	09 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 January 2018
Global end of trial reached?	Yes
Global end of trial date	09 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To provide an estimate (+/- 15%) of the progression-free survival (PFS) rate at 9 months, in pts without skin toxicity at 3 weeks (according to NCI CTCAE v. 4.0), treated with FOLFIRI + escalating dose of cetuximab (arm A). It is expected that the PFS rate will be similar to that observed after standard cetuximab treatment + FOLFIRI in pts with grade 1-4 skin toxicity in a K-Ras wild type population (CRYSTAL study).
Secondary objectives:
Safety profile of the combination in both treatment arms
Skin toxicity (correlations with outcome were not performed)
Response/disease control/duration of response: overall and in patients with liver-limited disease
PFS and OS
General resection rate and R0 resection rate for metastatic lesions
Pharmacokinetic parameters in selected centers only - not performed due to insufficient recruitment
Biomarker analyses: proteomics, microarray and PCR studies on plasma and tumour samples
Long term follow-up duration: 3 years from DB lock (9 July 2018)

Protection of trial subjects:

Ethics review and approval, informed consent. Premedication to prevent chemotherapy known adverse events (as per current practice and protocol recommendations), supportive care and routine monitoring.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 January 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Scientific research
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 4

Country: Number of subjects enrolled	Spain: 51
Country: Number of subjects enrolled	Belgium: 24
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Hungary: 22
Worldwide total number of subjects	108
EEA total number of subjects	108

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)	76
From 65 to 84 years	32
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

One hundred and eight patients were included. First patient enrolled: 18-Jan-2011. Last patient enrolled: 24-Mar-2014. End of recruitment: 8-Apr-2014. The study was deemed closed as of 30-Jun-2016. Last end of treatment assessment: 25-Jul-2016 and last follow-up data collected 10-Jan-2018. The database was locked on 9 July 2018.

Pre-assignment

Screening details:

The target population was represented by patients with unresectable metastatic colorectal cancer histologically confirmed, K-Ras wild type tumour, eligible for treatment with cetuximab in combination with irinotecan and 5-FU/LV in a first line setting. Patients were screened as per inclusion and exclusion criteria per protocol.

Period 1

Period 1 title	Full study duration:baseline-> follow-up (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Patients with no cetuximab-related skin toxicity or other significant toxicity after first 3 weeks of treatment with cetuximab standard dosing in combination with FOLFIRI, in whom cetuximab doses were increased at day 22.

Arm type	Experimental
Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	Erbitux (TM) Merck
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cetuximab 400 mg/m² (loading at day 1) followed by 250 mg/m² weekly on days 8 and 15. If no skin toxicity occurred at day 22 cetuximab was increased to 350mg/m², then to 500mg/m² at day 36. FOLFIRI (simplified de Gramont) starting at day 1, was given every second week: irinotecan 180mg/m², leucovorin 400 mg/m² (racemic) or 200 mg/m² (L-form), 5-FU 400 mg/m² bolus and 2400 mg/m² infusion over 46 hours. No dose escalation for FOLFIRI.

Arm title	Arm B

Arm description:

Patients with any grade cetuximab-related skin toxicity or other significant toxicity after first 3 weeks of treatment with cetuximab standard dosing in combination with FOLFIRI, in whom cetuximab doses were maintained at standard levels at day 22.

Arm type	Standard regimen longer than 3 weeks
Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	Erbitux (TM) Merck
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cetuximab 400 mg/m² (loading at day 1) followed by 250 mg/m² weekly from day 8 onwards. FOLFIRI (simplified de Gramont) starting at day 1, was given every second week: irinotecan 180mg/m², leucovorin 400 mg/m² (racemic) or 200 mg/m² (L-form), 5-FU 400 mg/m² bolus and 2400 mg/m²

infusion over 46 hours.

Arm title	Not allocated

Arm description:

Patients unable to continue treatment with cetuximab and FOLFIRI at standard or reduced doses, requiring discontinuation before arm allocation at day 22.

Arm type	Standard regimen less than 3 weeks
Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	Erbitux (TM) Merck
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cetuximab 400 mg/m² (loading at day 1) followed by 250 mg/m² weekly from day 8 onwards. FOLFIRI (simplified de Gramont) starting at day 1, was given every second week: irinotecan 180mg/m², leucovorin 400 mg/m² (racemic) or 200 mg/m² (L-form), 5-FU 400 mg/m² bolus and 2400 mg/m² infusion over 46 hours.

Number of subjects in period 1	Arm A	Arm B	Not allocated
Started	8	93	7
Completed	8	93	7

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description:	
Patients with no cetuximab-related skin toxicity or other significant toxicity after first 3 weeks of treatment with cetuximab standard dosing in combination with FOLFIRI, in whom cetuximab doses were increased at day 22.	
Reporting group title	Arm B
Reporting group description:	
Patients with any grade cetuximab-related skin toxicity or other significant toxicity after first 3 weeks of treatment with cetuximab standard dosing in combination with FOLFIRI, in whom cetuximab doses were maintained at standard levels at day 22.	
Reporting group title	Not allocated
Reporting group description:	
Patients unable to continue treatment with cetuximab and FOLFIRI at standard or reduced doses, requiring discontinuation before arm allocation at day 22.	

Reporting group values	Arm A	Arm B	Not allocated
Number of subjects	8	93	7
Age categorical Units: Subjects			
Adults (18-64 years)	2	69	5
From 65-84 years	6	24	2
Age continuous			
Age at first administration of cetuximab was considered. No split per age group was performed.			
Units: years			
median	66	60	64
full range (min-max)	57 to 76	30 to 79	58 to 77
Gender categorical Units: Subjects			
Female	5	24	1
Male	3	69	6
Primary tumour			
Right colon= caecum, ascending and transversum colon; left colon= descending and sigmoid colon.			
Units: Subjects			
Colon right	2	16	0
Colon left	2	47	5
Rectum	4	30	2
Tumour stage Units: Subjects			
T1	0	2	0
T2	0	2	0
T3	2	46	2
T4	4	27	4
Tx	2	16	1
Nodal stage Units: Subjects			
N0	2	7	2
N1	0	24	0

N2	3	34	2
Nx	3	28	3
ECOG PS Units: Subjects			
PS=0	6	48	1
PS=1	2	45	6
Metastases Units: Subjects			
Liver only	4	39	2
Liver + other	4	45	2
Other (no liver)	0	9	3
Index lesions Units: Subjects			
1 location	4	44	4
2 locations	2	28	1
>=3 locations	2	21	2
Prior cancer treatment Units: Subjects			
Chemotherapy only	0	4	1
Radiotherapy only	0	1	0
Surgery for primary tumour	1	10	0
Other / Combinations	2	5	0
No prior cancer treatment	5	73	6
Heart rate Units: Bpm			
arithmetic mean	76.7	77.7	84.5
full range (min-max)	58 to 103	44 to 105	64 to 105
Systolic blood pressure Units: mmHg			
arithmetic mean	120.9	129.7	126.6
full range (min-max)	78 to 145	90 to 194	88 to 180
Diastolic blood pressure Units: mmHg			
arithmetic mean	68.9	78.8	78.7
full range (min-max)	55 to 79	57 to 107	61 to 105

Reporting group values	Total		
Number of subjects	108		
Age categorical Units: Subjects			
Adults (18-64 years)	76		
From 65-84 years	32		
Age continuous			
Age at first administration of cetuximab was considered. No split per age group was performed.			
Units: years median full range (min-max)	- -		
Gender categorical Units: Subjects			
Female	30		
Male	78		

Primary tumour			
Right colon= caecum, ascending and transversum colon; left colon= descending and sigmoid colon.			
Units: Subjects			
Colon right	18		
Colon left	54		
Rectum	36		
Tumour stage Units: Subjects			
T1	2		
T2	2		
T3	50		
T4	35		
Tx	19		
Nodal stage Units: Subjects			
N0	11		
N1	24		
N2	39		
Nx	34		
ECOG PS Units: Subjects			
PS=0	55		
PS=1	53		
Metastases Units: Subjects			
Liver only	45		
Liver + other	51		
Other (no liver)	12		
Index lesions Units: Subjects			
1 location	52		
2 locations	31		
>=3 locations	25		
Prior cancer treatment Units: Subjects			
Chemotherapy only	5		
Radiotherapy only	1		
Surgery for primary tumour	11		
Other / Combinations	7		
No prior cancer treatment	84		
Heart rate Units: Bpm arithmetic mean full range (min-max)	--		
Systolic blood pressure Units: mmHg arithmetic mean full range (min-max)	--		
Diastolic blood pressure Units: mmHg arithmetic mean			

full range (min-max)	-		

Subject analysis sets

Subject analysis set title	ITT/Safety Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients for whom there was evidence they were administered any dose of cetuximab or FOLFIRI on study.
For this study, the safety set includes all patients and is identical to the intention-to-treat (ITT) set.

Reporting group values	ITT/Safety Set		
Number of subjects	108		
Age categorical Units: Subjects			
Adults (18-64 years)	76		
From 65-84 years	32		
Age continuous			
Age at first administration of cetuximab was considered. No split per age group was performed.			
Units: years median full range (min-max)	 60 30 to 79		
Gender categorical Units: Subjects			
Female	30		
Male	78		
Primary tumour			
Right colon= caecum, ascending and transversum colon; left colon= descending and sigmoid colon.			
Units: Subjects			
Colon right	18		
Colon left	54		
Rectum	36		
Tumour stage Units: Subjects			
T1	2		
T2	2		
T3	50		
T4	35		
Tx	19		
Nodal stage Units: Subjects			
N0	11		
N1	24		
N2	39		
Nx	34		
ECOG PS Units: Subjects			
PS=0	55		
PS=1	53		

Metastases Units: Subjects			
Liver only	45		
Liver + other	51		
Other (no liver)	12		
Index lesions Units: Subjects			
1 location	52		
2 locations	31		
>=3 locations	25		
Prior cancer treatment Units: Subjects			
Chemotherapy only	5		
Radiotherapy only	1		
Surgery for primary tumour	11		
Other / Combinations	7		
No prior cancer treatment	84		
Heart rate Units: Bpm			
arithmetic mean	78.0		
full range (min-max)	44 to 105		
Systolic blood pressure Units: mmHg			
arithmetic mean	128.9		
full range (min-max)	78 to 194		
Diastolic blood pressure Units: mmHg			
arithmetic mean	78.1		
full range (min-max)	55 to 107		

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description:	
Patients with no cetuximab-related skin toxicity or other significant toxicity after first 3 weeks of treatment with cetuximab standard dosing in combination with FOLFIRI, in whom cetuximab doses were increased at day 22.	
Reporting group title	Arm B
Reporting group description:	
Patients with any grade cetuximab-related skin toxicity or other significant toxicity after first 3 weeks of treatment with cetuximab standard dosing in combination with FOLFIRI, in whom cetuximab doses were maintained at standard levels at day 22.	
Reporting group title	Not allocated
Reporting group description:	
Patients unable to continue treatment with cetuximab and FOLFIRI at standard or reduced doses, requiring discontinuation before arm allocation at day 22.	
Subject analysis set title	ITT/Safety Set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients for whom there was evidence they were administered any dose of cetuximab or FOLFIRI on study. For this study, the safety set includes all patients and is identical to the intention-to-treat (ITT) set.	

Primary: Progression free survival (PFS) rate at 9 months

End point title	Progression free survival (PFS) rate at 9 months
End point description:	
The PFS rate at 9 months is defined as the Kaplan-Meier estimate of the probability of being alive and free of progression at 9 months. All patients (ITT).	
End point type	Primary
End point timeframe:	
Treatment + follow-up (3 years from database lock)	

End point values	Arm A	Arm B	Not allocated	ITT/Safety Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	8	93	7	108
Units: %	45	58	0	55

Statistical analyses

Statistical analysis title	Progression free survival (PFS) rate at 9 months
Statistical analysis description:	
Proportion estimates from Kaplan-Meier analysis and 95% CI were: Arm A: 45.0 [8.1;81.9]; Arm B: 58.3 [47.3;69.3]; Not allocated: 0.0 [0.0;0.0]; ITT/Safety Set: 55.0 [44.6;65.4]. No formal statistical comparison between groups was performed. Details on PFS definition are provided in attached documents. Detailed data available upon request.	
Comparison groups	Arm A v Arm B v Not allocated

Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	percentage
Point estimate	55
Confidence interval	
level	95 %
sides	2-sided
lower limit	44.6
upper limit	65.4
Variability estimate	Standard deviation

Notes:

[1] - Proportion estimates from Kaplan-Meier.

Secondary: Progression free survival (PFS) median time

End point title	Progression free survival (PFS) median time

End point description:

Progression free survival time was considered from start of treatment until the first observation of disease progression or death from any cause, whichever occurred first. All patients (ITT).

End point type	Secondary

End point timeframe:

Treatment + follow-up (3 years from database lock)

End point values	Arm A	Arm B	Not allocated	ITT/Safety Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	8	93	7	108
Units: Months				
median (confidence interval 95%)	8.8 (6.2 to 25.6)	11.5 (8.2 to 14.0)	1.3 (0.9 to 1.5)	10.7 (8.1 to 13.7)

Statistical analyses

Statistical analysis title	PFS median time (all patients)

Statistical analysis description:

Kaplan-Meier analysis.
No formal statistical comparison between groups was performed.
Details on PFS definition are provided in attached documents.
Detailed data available upon request.

Comparison groups	Arm A v Arm B v Not allocated
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	Months
Point estimate	10.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	8.1
upper limit	13.7
Variability estimate	Standard deviation

Notes:

[2] - Kaplan-Meier.

Secondary: Progression free survival (PFS) median time for resected patients

End point title	Progression free survival (PFS) median time for resected patients[3]

End point description:

Progression free survival time was considered from start of treatment until the first observation of disease progression or death from any cause, whichever occurred first. This is the subset of resected patients (resection of secondary lesions with curative intent was performed). Patients resected after they started subsequent anti-cancer treatment (600-01-006 and 600-04-006) or after progression on treatment (100-02-002, 200-03-001, and 600-01-038) were not considered as 'resected for metastatic lesions on study'. Patients were not censored at time of surgery. See appendix 3 for definitions of PFS.

End point type	Secondary

End point timeframe:

Treatment + follow-up (3 years from database lock)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: There were no resected patients among the patients in the arm "not allocated". This is a subset analysis.

End point values	Arm A	Arm B	ITT/Safety Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	1	16	17	
Units: Months				
median (confidence interval 95%)	11.3 (0 to 999)	14.5 (12.7 to 17.9)	14.2 (11.3 to 17.9)	

Statistical analyses

Statistical analysis title	PFS median time (resected patients)

Statistical analysis description:

Kaplan-Meier analysis.
If median and/or 95% CI was not estimable, code 999 was entered.
No formal statistical comparison between groups was performed.
Details on PFS definition are provided in attached documents.
Detailed data available upon request.

Comparison groups	Arm A v Arm B
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other[4]
Parameter estimate	Months
Point estimate	14.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	11.3
upper limit	17.9
Variability estimate	Standard deviation

Notes:

[4] - Kaplan-Meier.

Secondary: Progression free survival (PFS) time for resected versus non-resected patients (hazard ratio)

End point title	Progression free survival (PFS) time for resected versus non-resected patients (hazard ratio)

End point description:

Progression free survival time was considered from start of treatment until the first observation of disease progression or death from any cause, whichever occurred first. This is the subset of resected patients (resection of secondary lesions with curative intent was performed). Patients resected after they started subsequent anti-cancer treatment (600-01-006 and 600-04-006) or after progression on treatment (100-02-002, 200-03-001, and 600-01-038) were not considered as 'resected for metastatic lesions on study'. Patients were not censored at time of surgery. See appendix 3 for definitions of PFS.

End point type	Secondary

End point timeframe:

Treatment + follow-up (3 years from database lock)

End point values	Arm A	Arm B	Not allocated	ITT/Safety Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	8	93	7	108
Units: Hazard ratio				
number (confidence interval 95%)	1.17 (0.13 to 10.60)	0.82 (0.48 to 1.42)	999 (999 to 999)	0.79 (0.47 to 1.34)

Statistical analyses

Statistical analysis title	PFS time resected versus non-resected patients

Statistical analysis description:

Cox proportional hazard.
If Hazard ratio was not available (no resections performed) and 95% CI was not estimable, code 999 was entered.
Number of resected patients were: Arm A: 1; Arm B: 16; Not allocated: 0; ITT/Safety Set: 17.
Number of not-resected patients were: Arm A: 7; Arm B: 77; Not allocated: 7; ITT/Safety Set: 91.
No formal statistical comparison between groups was performed.
Details on PFS definition are provided in attached documents.
Detailed data available upon request.

Comparison groups	Arm A v Arm B v Not allocated

Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	other[5]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	1.34
Variability estimate	Standard deviation

Notes:

[5] - Cox proportional hazard.

Secondary: Death rates by 3 years follow-up

End point title	Death rates by 3 years follow-up

End point description:

Deaths by 3 years follow-up after last cetuximab administration + 30 days. All patients (ITT).

End point type	Secondary

End point timeframe:

Treatment + follow-up (3 years from database lock)

End point values	Arm A	Arm B	Not allocated	ITT/Safety Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	8	93	7	108
Units: Number of subjects				
Deceased	6	65	7	78
Alive after 3 years follow-up	2	16	0	18
Lost to follow-up before 3 years follow-up	0	12	0	12

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS) median time

End point title	Overall survival (OS) median time

End point description:

Overall survival was considered from start of treatment to death. All patients (ITT).

End point type	Secondary

End point timeframe:

Treatment + follow-up (3 years from database lock)

End point values	Arm A	Arm B	Not allocated	ITT/Safety Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	8	93	7	108
Units: Months				
median (confidence interval 95%)	28.4 (12.0 to 999)	31.4 (25.5 to 34.9)	4.9 (1.0 to 12.5)	29.8 (22.4 to 33.3)

Statistical analyses

Statistical analysis title	OS median time (all patients)

Statistical analysis description:

Kaplan-Meier analysis. If median and/or 95% CI was not estimable, code 999 was entered.
No formal statistical comparison between groups was performed.
Detailed data available upon request.

Comparison groups	Arm A v Arm B v Not allocated
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	other[6]
Parameter estimate	Months
Point estimate	29.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	22.4
upper limit	33.3
Variability estimate	Standard deviation

Notes:

[6] - Kaplan-Meier.

Secondary: Overall survival (OS) median time for resected patients

End point title	Overall survival (OS) median time for resected patients[7]

End point description:

Overall survival was considered from start of treatment to death. Subset of resected patients (resection of secondary lesions with curative intent was performed). Patients resected after they started subsequent anti-cancer treatment (600-01-006 and 600-04-006) or after progression (100-02-002, 200-03-001, and 600-01-038) were not considered as 'resected for metastatic lesions on study'.

End point type	Secondary

End point timeframe:

Treatment + follow-up (3 years from database lock)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There were no resected patients among the patients in the arm "not allocated". This is a subset analysis.

End point values	Arm A	Arm B	ITT/Safety Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	1	16	17	
Units: Months				
median (confidence interval 95%)	999 (999 to 999)	999 (32.7 to 999)	999 (32.7 to 999)	

Statistical analyses

Statistical analysis title	OS median time (resected patients)

Statistical analysis description:

Kaplan-Meier analysis.
If median and/or 95% CI was not estimable, code 999 was entered.
No formal statistical comparison between groups was performed.
Detailed data available upon request.

Comparison groups	Arm A v Arm B
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other[8]
Parameter estimate	Counts
Point estimate	999
Confidence interval	
level	95 %
sides	2-sided
lower limit	32.7
upper limit	999
Variability estimate	Standard deviation

Notes:

[8] - Kaplan-Meier.

Secondary: Overall response

End point title	Overall response

End point description:

Overall response is defined as the best tumor response on treatment of either complete response (CR) or partial response (PR) (CR + PR).
Tumor response is based on the assessments (CT/MRI) for target and non-target lesions as well as considering the occurrence of new lesions as per RECIST criteria. All patients (ITT).

End point type	Secondary

End point timeframe:

Treatment

End point values	Arm A	Arm B	Not allocated	ITT/Safety Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	8	93	7	108
Units: Number of subjects				
CR or PR	6	64	0	70
Other (SD, PD, not evaluable, missing)	2	29	7	38

Statistical analyses

Statistical analysis title	Overall response

Statistical analysis description:

Descriptive. Rates of overall response (CR or PR) with confidence intervals were calculated per arm: Arm A: 75.0% [34.9%;96.8%]; Arm B: 68.8% [58.4%;78.0%]; Not allocated: 0.0% [0.0%;41.0%]; ITT/Safety Set: 64.8% [55.0%;73.8%].
No formal statistical comparison between arms was performed.
Detailed data available upon request.

Comparison groups	Arm A v Arm B v Not allocated
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	other[9]
Parameter estimate	percentage
Point estimate	64.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	55
upper limit	73.8
Variability estimate	Standard deviation

Notes:

[9] - Descriptive.

Secondary: Overall response in patients with liver-limited disease

End point title	Overall response in patients with liver-limited disease

End point description:

Overall response is defined as the best tumor response on treatment of either complete response (CR) or partial response (PR) (CR + PR).
Tumor response is based on the assessments (CT/MRI) for target and non-target lesions as well as considering the occurrence of new lesions as per RECIST criteria. Subset of patients with liver-limited disease.

End point type	Secondary

End point timeframe:

Treatment

End point values	Arm A	Arm B	Not allocated	ITT/Safety Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	4	39	2	45
Units: Number of subjects				
CR or PR	2	30	0	32
Other (SD, PD, missing)	2	9	2	13

Statistical analyses

Statistical analysis title	Overall response (liver-limited disease)

Statistical analysis description:

Descriptive. Rates of overall response (CR or PR) with confidence intervals were calculated per arm: Arm A: 50.0% [6.8%;93.2%]; Arm B: 76.9% [60.7%;88.9%]; Not allocated: 0.0% [0.0%;84.2%]; ITT/Safety Set: 71.1% [55.7%;83.6%].
No formal statistical comparison between arms was performed.
Detailed data available upon request.

Comparison groups	Arm A v Arm B v Not allocated
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other[10]
Parameter estimate	percentage
Point estimate	71.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	55.7
upper limit	83.6
Variability estimate	Standard deviation

Notes:

[10] - Descriptive.

Secondary: Disease control

End point title	Disease control

End point description:

Disease control is defined as a best response on treatment (e.g. till end of treatment evaluation) of either complete response (CR), partial response (PR), or stable disease (SD) (CR + PR + SD). RECIST criteria (CT/MRI). All patients (ITT).

End point type	Secondary

End point timeframe:

Treatment

End point values	Arm A	Arm B	Not allocated	ITT/Safety Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	8	93	7	108
Units: Number of subjects				
CR, PR, or SD	8	84	0	92
Other (PD, not evaluable, missing)	0	9	7	16

Statistical analyses

Statistical analysis title	Counts of disease control

Statistical analysis description:

Descriptive. Rates of disease control (CR, PR, or SD) with confidence intervals were calculated per arm: Arm A: 100% [63.1%;100%]; Arm B: 90.3% [82.4%;95.5%]; Not allocated: 0.0% [0.0%;41.0%]; ITT/Safety Set: 85.2% [77.1%;91.3%]
No formal statistical comparison between groups was performed.
Detailed data available upon request.

Comparison groups	Arm A v Arm B v Not allocated
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	other[11]
Parameter estimate	Counts
Point estimate	85.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	77.1
upper limit	91.3
Variability estimate	Standard deviation

Notes:

[11] - Descriptive.

Secondary: Duration of response

End point title	Duration of response[12]

End point description:

The duration of response in responding patients is defined as the time interval from the time measurement criteria are first met for CR/PR during treatment to either the first time disease progression is documented or death. Subset of responders.

End point type	Secondary

End point timeframe:

Treatment + follow-up (3 years from database lock)

Notes:

[12] - 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: There were no responders among the patients in the arm "not allocated". This is a subset analysis.

End point values	Arm A	Arm B	ITT/Safety Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	6	64	70	
Units: Months				
median (confidence interval 95%)	8.3 (3.6 to 24.2)	11.7 (9.7 to 14.6)	11.7 (8.6 to 15.4)	

Statistical analyses

Statistical analysis title	Duration of response

Statistical analysis description:

Kaplan-Meier analysis of duration of response for the patients with an assessment of CR or PR at any

time during the study.
No formal statistical comparison between groups was performed.
Detailed data available upon request.

Comparison groups	Arm A v Arm B
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	other[13]
Parameter estimate	Months
Point estimate	11.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.6
upper limit	15.4
Variability estimate	Standard deviation

Notes:

[13] - Kaplan-Meier

Secondary: Disease control in patients with liver-limited disease

End point title	Disease control in patients with liver-limited disease

End point description:

Disease control is defined as a best response on treatment (e.g. till end of treatment evaluation) of either complete response (CR), partial response (PR), or stable disease (SD) (CR + PR + SD). RECIST criteria (CT/MRI). Subset of patients with liver-limited disease.

End point type	Secondary

End point timeframe:

Treatment

End point values	Arm A	Arm B	Not allocated	ITT/Safety Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	4	39	2	45
Units: Number of subjects				
CR, PR, or SD	4	37	0	41
Other (PD, missing)	0	2	2	4

Statistical analyses

Statistical analysis title	Counts of disease control (liver-limited disease)

Statistical analysis description:

Descriptive. Rates of disease control (CR, PR, or SD) with confidence intervals were calculated per arm: Arm A: 100% [39.8%;100%]; Arm B: 94.9% [82.7%;99.4%]; Not allocated: 0.0% [0.0%;84.2%]; ITT/Safety Set: 91.1% [78.8%;97.5%].
No formal statistical comparison between groups was performed.
Detailed data available upon request.

Comparison groups	Arm A v Arm B v Not allocated

Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other[14]
Parameter estimate	Counts
Point estimate	91.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	78.8
upper limit	97.5
Variability estimate	Standard deviation

Notes:

[14] - Descriptive.

Secondary: Duration of response in liver-limited disease patients

End point title	Duration of response in liver-limited disease patients[15]

End point description:

The duration of response in responding patients is defined as the time interval from the time measurement criteria are first met for CR/PR during treatment to either the first time disease progression is documented or death. Subset of responders among patients with liver-limited disease.

End point type	Secondary

End point timeframe:

Treatment + follow-up (3 years from database lock)

Notes:

[15] - 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: There were no responders among the patients in the arm "not allocated". This is a subset analysis.

End point values	Arm A	Arm B	ITT/Safety Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	2	30	32	
Units: Months				
median (confidence interval 95%)	13.9 (3.6 to 24.2)	11.1 (7.6 to 13.0)	11.1 (7.6 to 22.5)	

Statistical analyses

Statistical analysis title	Duration of response (liver-limited disease)

Statistical analysis description:

Kaplan-Meier analysis of duration of response for the patients with an assessment of CR or PR at any time during the study.
No formal statistical comparison between groups was performed.
Detailed data available upon request.

Comparison groups	Arm A v Arm B

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other[16]
Parameter estimate	Months
Point estimate	11.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.6
upper limit	22.5
Variability estimate	Standard deviation

Notes:

[16] - Kaplan-Meier.

Secondary: Resections for metastatic lesions

End point title	Resections for metastatic lesions

End point description:

All patients were deemed non-resectable at baseline but some became resectable during or post-treatment. All patients (ITT). Only those patients in whom resection of secondary lesions with curative intent was performed were considered as 'resected'. Patients resected after they started subsequent anti-cancer treatment (600-01-006 and 600-04-006) or after progression (100-02-002, 200-03-001, and 600-01-038) were not considered as 'resected for metastatic lesions on study'.

End point type	Secondary

End point timeframe:

Treatment + follow-up (3 years from database lock)

End point values	Arm A	Arm B	Not allocated	ITT/Safety Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	8	93	7	108
Units: Number of subjects				
Resected (surgery with curative intent performed)	1	16	0	17
Non-resected	7	77	7	91

Statistical analyses

No statistical analyses for this end point

Secondary: R0 rate (free of tumor after resection for metastatic lesions)

End point title	R0 rate (free of tumor after resection for metastatic lesions)[17]

End point description:

Rate of patients free of tumor after surgery. Subset of resected patients (resection of secondary lesions with curative intent was performed). Patients resected after they started subsequent anti-cancer treatment (600-01-006 and 600-04-006) or after progression (100-02-002, 200-03-001, and 600-01-038) were not considered as 'resected for metastatic lesions on study'.

End point type	Secondary

End point timeframe:

Treatment + follow-up (3 years from database lock)

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: There were no resected patients among the patients in the arm "not allocated". This is a subset analysis.

End point values	Arm A	Arm B	ITT/Safety Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	1	16	17	
Units: Number of subjects				
Free of tumor	1	12	13	
Not free of tumor	0	4	4	

Statistical analyses

No statistical analyses for this end point

Secondary: Skin toxicity (safety)

End point title	Skin toxicity (safety)

End point description:

Treatment-emergent adverse events identified by the investigator as skin reaction or events with description skin infection or nail infection. These events were not always considered by the investigator for arm allocation:
Arm A:
Patient 100-09-002 - Rash acneiform (Minimal redness of skin of the forehead) unrelated to cetuximab and patient 100-11-001 - Rash acneiform (only on the chin) lasting 5 days during the first 3 weeks, possibly related to cetuximab: These patients were escalated notwithstanding these events.
Arm B:
Patient 300-07-001 was not escalated though at Infusion visit 4, no skin reaction grade 1 or higher had appeared.

Worst grade per patient. All patients treated (Safety).

End point type	Secondary

End point timeframe:

From signature of informed consent to end of treatment visit plus 30 days.

End point values	Arm A	Arm B	Not allocated	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	93	7	
Units: Number of subjects				
Any (onset prior to arm allocation)	2	92	3	
Any (all times)	7	93	3	
Grade 1	0	19	2	
Grade 2	5	44	1	
Grade 3	2	30	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory safety assessments

End point title	Laboratory safety assessments

End point description:

Severe laboratory abnormalities (hematology and biochemistry grade 3 and higher). Worst grade per patient. All patients treated (Safety).

End point type	Secondary

End point timeframe:

From signature of informed consent to end of treatment visit plus 30 days.

End point values	Arm A	Arm B	Not allocated	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	93	7	
Units: Number of subjects				
Hemoglobin decreased	0	3	0	
White blood cell count decreased	3	8	0	
Neutrophils decreased	3	19	0	
Lymphocytes decreased	2	6	0	
Platelet count decreased	0	2	0	
Bilirubin increased	0	3	0	
ALAT increased	0	2	0	
ASAT increased	0	1	0	
ALP increased	2	4	0	
Sodium decreased	1	3	1	
Potassium decreased	2	7	0	
Magnesium decreased	1	2	0	
Magnesium increased	0	1	0	
Serum calcium decreased	0	2	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Deaths till 30 days from last cetuximab administration

End point title	Deaths till 30 days from last cetuximab administration

End point description:

Deaths of all causes occuring between the signature of consent and the date of last cetuximab

administration + 30 days are listed per arm. None of these fatalities were deemed related to the investigational drug. Details are provided in attached documents.

End point type	Secondary

End point timeframe:

From signature of informed consent to last cetuximab administration plus 30 days.

End point values	Arm A	Arm B	Not allocated	ITT/Safety Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	8	93	7	108
Units: Number of subjects				
All causes	1	6	2	9
Colonic perforation	1	0	0	1
Malaise	0	1	0	1
Bronchial infection	0	1	0	1
Lung infection	0	1	0	1
Circulatory failure	0	1	0	1
Cardiac arrest	0	1	0	1
Colonic obstruction	0	1	0	1
Peritoneal infection	0	0	1	1
Ileus	0	0	1	1

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signature of informed consent to end of treatment visit plus 30 days.

Adverse event reporting additional description:

SAEs occurring between ICF signature and EOT+30 days are listed. Fatalities are entered if occurred within 30 days from last drug administration. All severe AEs (grade 3-5) including SAEs, are listed in the non-serious AE table. Skin toxicity and severe lab abnormalities are further detailed in section End points.

Assessment type	Systematic

Dictionary used

Dictionary name	NCI-CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Arm A

Reporting group description:

Patients with no cetuximab-related skin toxicity or other significant toxicity after first 3 weeks of treatment with cetuximab standard dosing in combination with FOLFIRI, in whom cetuximab doses were increased at day 22.

Reporting group title	Arm B

Reporting group description:

Patients with any grade cetuximab-related skin toxicity or other significant toxicity after first 3 weeks of treatment with cetuximab standard dosing in combination with FOLFIRI, in whom cetuximab doses were maintained at standard levels at day 22.

Reporting group title	Not allocated

Reporting group description:

Patients unable to continue treatment with cetuximab and FOLFIRI at standard or reduced doses, requiring discontinuation before arm allocation at day 22.

Serious adverse events	Arm A	Arm B	Not allocated
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 8 (75.00%)	39 / 93 (41.94%)	6 / 7 (85.71%)
number of deaths (all causes)	1	6	2
number of deaths resulting from adverse events	1	6	2
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2
White blood cell decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2

Vascular disorders			
Circulatory failure			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2
Thromboembolic event			
subjects affected / exposed	0 / 8 (0.00%)	8 / 93 (8.60%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	1 / 8	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2
Ventricular fibrillation			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2
Nervous system disorders			
Ischemia cerebrovascular			
subjects affected / exposed	0 / 8 (0.00%)	0 / 93 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 8 (12.50%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2
Fever			
subjects affected / exposed	1 / 8 (12.50%)	0 / 93 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2
Malaise			

subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2
Immune system disorders			
Anaphylaxis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 8 (0.00%)	3 / 93 (3.23%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2
Colonic hemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2
Colonic obstruction			
subjects affected / exposed	0 / 8 (0.00%)	3 / 93 (3.23%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2
Colonic perforation			
subjects affected / exposed	1 / 8 (12.50%)	1 / 93 (1.08%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2
Diarrhea			
subjects affected / exposed	2 / 8 (25.00%)	2 / 93 (2.15%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	2 / 2	2 / 3	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2
Enterocolitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2
Ileus			

subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2
Jejunal obstruction			
subjects affected / exposed	1 / 8 (12.50%)	0 / 93 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2
Rectal hemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2
Small intestinal obstruction			
subjects affected / exposed	0 / 8 (0.00%)	3 / 93 (3.23%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 5	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2
Hepatobiliary disorders			
Gallbladder obstruction			
subjects affected / exposed	0 / 8 (0.00%)	2 / 93 (2.15%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2
Hepatic hematoma			
subjects affected / exposed	1 / 8 (12.50%)	0 / 93 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2
Portal vein thrombosis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2
Respiratory, thoracic and mediastinal disorders			
Respiratory insufficiency			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2

Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2
Infections and infestations			
Bronchial infection			
subjects affected / exposed	0 / 8 (0.00%)	2 / 93 (2.15%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2
Catheter related infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2
Enterocolitis infectious			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2
Erysipelas			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2
Kidney infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2
Lung infection			
subjects affected / exposed	0 / 8 (0.00%)	3 / 93 (3.23%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2
Pelvic infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2

Peritoneal infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 93 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2
Sepsis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2
Urinary tract infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2
Yersinia enterocolitica gastroenteritis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2
Metabolism and nutrition disorders			
Diabetes angiopathy			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2
Severe undernutrition			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 6	0 / 2

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

Non-serious adverse events	Arm A	Arm B	Not allocated
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 8 (75.00%)	66 / 93 (70.97%)	3 / 7 (42.86%)
Vascular disorders			
Circulatory failure			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences (all)	0	1	0

Thromboembolic event			
subjects affected / exposed	0 / 8 (0.00%)	11 / 93 (11.83%)	0 / 7 (0.00%)
occurrences (all)	0	11	0
General disorders and administration site conditions			
General deterioration			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	0 / 8 (0.00%)	3 / 93 (3.23%)	0 / 7 (0.00%)
occurrences (all)	0	5	0
Immune system disorders			
Anaphylaxis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Pulmonary edema			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Respiratory failure			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Dyspnea			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Respiratory insufficiency			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Investigations			
Weight gain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Ventricular fibrillation			

subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 8 (12.50%)	0 / 93 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Syncope			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	0 / 8 (0.00%)	3 / 93 (3.23%)	0 / 7 (0.00%)
occurrences (all)	0	5	0
Febrile neutropenia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 93 (2.15%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Leukocytosis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Colonic haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Hemorrhoids			
subjects affected / exposed	1 / 8 (12.50%)	0 / 93 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Colonic obstruction			
subjects affected / exposed	0 / 8 (0.00%)	3 / 93 (3.23%)	0 / 7 (0.00%)
occurrences (all)	0	4	0
Diarrhea			
subjects affected / exposed	2 / 8 (25.00%)	14 / 93 (15.05%)	0 / 7 (0.00%)
occurrences (all)	2	20	0
Ileus			

subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Colonic perforation			
subjects affected / exposed	1 / 8 (12.50%)	1 / 93 (1.08%)	1 / 7 (14.29%)
occurrences (all)	1	1	1
Small intestinal obstruction			
subjects affected / exposed	0 / 8 (0.00%)	2 / 93 (2.15%)	1 / 7 (14.29%)
occurrences (all)	0	2	1
Jejunal obstruction			
subjects affected / exposed	1 / 8 (12.50%)	0 / 93 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Mucositis oral			
subjects affected / exposed	0 / 8 (0.00%)	3 / 93 (3.23%)	0 / 7 (0.00%)
occurrences (all)	0	3	0
Vomiting			
subjects affected / exposed	0 / 8 (0.00%)	2 / 93 (2.15%)	1 / 7 (14.29%)
occurrences (all)	0	2	1
Hepatobiliary disorders			
Gallbladder obstruction			
subjects affected / exposed	0 / 8 (0.00%)	2 / 93 (2.15%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Hepatic hematoma			
subjects affected / exposed	1 / 8 (12.50%)	0 / 93 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Portal vein thrombosis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Hepatic pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Hypertrichosis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 93 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Fissure/feet			

subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Fissure/fingers			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	0 / 8 (0.00%)	2 / 93 (2.15%)	0 / 7 (0.00%)
occurrences (all)	0	3	0
Rash maculo-papular			
subjects affected / exposed	0 / 8 (0.00%)	2 / 93 (2.15%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Rash acneiform			
subjects affected / exposed	0 / 8 (0.00%)	17 / 93 (18.28%)	0 / 7 (0.00%)
occurrences (all)	0	25	0
Skin hyperpigmentation			
subjects affected / exposed	1 / 8 (12.50%)	0 / 93 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Bronchial infection			
subjects affected / exposed	0 / 8 (0.00%)	2 / 93 (2.15%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Enterocolitis infectious			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Acute cytolysis due to viral infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Erysipelas			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Lung infection			

subjects affected / exposed	0 / 8 (0.00%)	3 / 93 (3.23%)	0 / 7 (0.00%)
occurrences (all)	0	3	0
Paronychia			
subjects affected / exposed	2 / 8 (25.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences (all)	2	3	0
Catheter related infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Kidney infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Papulopustular rash			
subjects affected / exposed	0 / 8 (0.00%)	7 / 93 (7.53%)	0 / 7 (0.00%)
occurrences (all)	0	16	0
Skin infection			
subjects affected / exposed	1 / 8 (12.50%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Pelvic infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Peritoneal infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 93 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Yersinia enterocolitica gastroenteritis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Sepsis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	1 / 8 (12.50%)	2 / 93 (2.15%)	0 / 7 (0.00%)
occurrences (all)	1	3	0
Diabetes angiopathy			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences (all)	0	1	0

Hypokalemia			
subjects affected / exposed	2 / 8 (25.00%)	2 / 93 (2.15%)	0 / 7 (0.00%)
occurrences (all)	4	7	0
Dehydration			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Hyperglycemia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 93 (2.15%)	0 / 7 (0.00%)
occurrences (all)	0	4	0
Hypophosphatemia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 93 (2.15%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Hyponatremia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences (all)	2	1	0
Hypomagnesemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 93 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Severe undernutrition			
subjects affected / exposed	0 / 8 (0.00%)	1 / 93 (1.08%)	0 / 7 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 May 2013	The amendment consisted mainly of reducing the total sample size from the initially planned 375 patients to 130 patients in two study arms due to general slow accrual. The amended protocol and amended ICF have been approved in all participating countries during the year 2013.
01 April 2016	Recruitment was stopped at 108 patients in April 2014 due to slow accrual that determined a much longer duration than limited academic financial resources could sustain. In March 2016, there were 2 patients in Spain still receiving treatment. The amendment of April 2016, submitted in Spain only, was necessary to early terminate the trial while these patients were actively receiving study medication. Arrangements had been made for them to continue treatment outside of trial.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
07 January 2013	Temporary interruption due to administrative reasons (change of CRO in charge for project management and pharmacovigilance).	05 February 2013

Notes:

Limitations and caveats

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

Insufficient population in escalation arm A as early skin toxicity in most patients; study not powered for formal comparison between arms. Systematic error sources: some AEs re-coded by sponsor, misclassification bias (local response assessment).

Notes: