Clinical trial results:
Phase II Study for the Evaluation of the Efficacy of Gemcitabine plus Erlotinib in Rash-positive Patients with Metastatic Pancreatic Cancer and Good Risk Factors

Summary

EudraCT number	2011-005471-17
Trial protocol	DE
Global end of trial date	01 February 2017

Results information

Result version number	v1 (current)
This version publication date	16 June 2018
First version publication date	16 June 2018

Trial information

Trial identification

Sponsor protocol code	RASH

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01729481
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Klinikum der Universität München-Großhadern
Sponsor organisation address	Marchioninistr. 15, München, Germany, 81377
Public contact	Study office, Klinikum der Universität München-Großhadern, 49 89440072208, Matthias.Wolff@med.uni-muenchen.de
Scientific contact	Study office, Klinikum der Universität München-Großhadern, 49 89440072208, Matthias.Wolff@med.uni-muenchen.de

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	16 August 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 February 2017
Global end of trial reached?	Yes
Global end of trial date	01 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1-year survival rate of "good risk" patients who develop rash under treatment with gemcitabine/erlotinib

Protection of trial subjects:

This clinical study was designed and implemented and reported in accordance with the International Conference on Harmonisation (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable European and national regulations (including European Directive 2001/20/EC and German Drug Law (AMG)) and with the ethical principles laid down in the Declaration of Helsinki. Participating subjects signed the informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision.

Background therapy:

Not applicable.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	11 July 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 150
Worldwide total number of subjects	150
EEA total number of subjects	150

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)	88

From 65 to 84 years	62
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

25 investigational sites in Germany were participating. 150 subjects were screened and enrolled at 20 of these 25 investigational sites.
The first patient was enrolled 11-July-2012, the last patient 6-July-2015.

Pre-assignment

Screening details:

Main inclusion criteria:
- Histologically confirmed metastatic adenocarcinoma of the pancreas (UICC stadium IV; any T, any N, M1 following TNM)
- At least one measurable tumor lesion (CT or MRI) according to RECIST version 1.1
- ECOG PS 0 and 1
- Between 18 and 75 years of age
- Bilirubin ≤ 1.5 ULN (biliary stent permitted)

Pre-assignment period milestones

Number of subjects started	150
Number of subjects completed	144

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Violation in-/exclusion criteria (retrospectively): 1
Reason: Number of subjects	Death: 1
Reason: Number of subjects	Progression of tumor disease: 1
Reason: Number of subjects	Patient's wish: 1
Reason: Number of subjects	Loss of contact: 1
Reason: Number of subjects	Consent withdrawn by subject: 1

Period 1

Period 1 title	Run-in with Gemcitabin/Erlotinib
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Run-in

Arm description:

Treatment with gemcitabine 1000 mg/^2 BSA weekly and erlotinib, 100 mg once daily for 4 weeks. Treatment was discontinued earlier in case of progression of the metastatic pancreatic adenocarcinoma, unacceptable toxicity or other reasons (patient’s wish, investigator’s decision).

Arm type	Run-in
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

1000 mg/m^2 on D1, D8, D15, D21 of one 28-day cycle.

Investigational medicinal product name	Erlotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

100 mg once daily for 28 days.

Number of subjects in period 1[1]	Run-in
Started	144
Completed	116
Not completed	28
Physician decision	6
Adverse event, non-fatal	3
Patient's wish	7
Death	5
Progression of tumor disease	7

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Sample size calculation of 150 patients included 10% drop-outs. As 6 patients were screening failures , 144 patients entered the Run-in phase.

Period 2

Period 2 title	Treatment according to ocurrence of rash
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A (rash-positve)

Arm description:

Patient who had developed skin rash after 4 weeks of treatment with gemcitabine 1000 mg/^2 BSA weekly and erlotinib 100 mg p.o. once daily in the Run-in phase (first 4 treatment weeks), continued treatment with gemcitabine 1000 mg/^2 weekly on D1, D7, D14 of each 28-day treatment cycle and erlotinib 100 mg p.o. once daily.
Treatment was continued until progression of the metastatic pancreatic adenocarcinoma, unacceptable toxicity or other reasons (patient’s wish, investigator’s decision).

Arm type	Experimental
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

1000 mg/m^2 BSA on D1, D8, D15 of each 28-day cycle

Investigational medicinal product name	Erlotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

100 mg once daily

Arm title	Arm B (rash-negative)

Arm description:

Patient who had developed no skin rash after 4 weeks of treatment with gemcitabine 1000 mg/^2 BSA weekly and erlotinib 100 mg p.o. once daily in the Run-in phase (first 4 treatment weeks), received further treatment with FOLFIRINOX (fluorouracil, folinic acid, irinotecan, oxaliplatin). Treatment was continued until progression of the metastatic pancreatic adenocarcinoma, unacceptable toxicity or other reasons (patient's wish, investigator's decision). Only rash-negative patients who were given FOLFIRINOX treatment after Run-in are included.

Arm type	treatment choice for RASH-negative patients
Investigational medicinal product name	Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection, Solvent for solution for infusion
Routes of administration	Intravenous bolus use , Intravenous drip use

Dosage and administration details:

400 mg/m^2 BSA as bolus injection, followed by 2400 mg/m^2 BSA as continuous infusion over about 48 hours on D1/D2 of a 14-day cycle.

Investigational medicinal product name	Folinic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion, Solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

400 mg/m^2 BSA as intravenous infusion over about 2 hours on D1 of a 14-day cycle.

Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

180 mg/m^2 BSA as intravenous infusion over about 90 minutes on D1 of a 14-day cycle.

Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

85 mg/m^2 BSA as intravenous infusion over about 2 hours on D1 of a 14-day cycle.

Number of subjects in period 2	Arm A (rash-positve)	Arm B (rash-negative)
Started	89	27
Completed	89	27

Baseline characteristics

Reporting groups

Reporting group title	Run-in with Gemcitabin/Erlotinib

Reporting group description:

All patients of the Full-Analysis Population, who were administered at least one dose of gemcitabine or erlotinib during the Run-in period (first four weeks of treatment)

Reporting group values	Run-in with Gemcitabin/Erlotinib	Total	
Number of subjects	144	144	
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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
median	63.5		
full range (min-max)	24.0 to 75.0	-	
Gender categorical Units: Subjects			
Female	57	57	
Male	87	87	
ECOG Performance Status Units: Subjects			
ECOG PS 0	87	87	
ECOG PS 1	57	57	

Subject analysis sets

Subject analysis set title	Rash-positive (primary endpoint)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients, who are rash-positive after 4 weeks treatment with gemcitabine and erlotinib (all except one patient continued treatment with gemcitabine and erlotinib after the Run-in phase)

Subject analysis set title	Patients - efficacy assessable
Subject analysis set type	Per protocol

Subject analysis set description:

Patients of Full Analysis Set with: (a) at least two cycles for patients in arm A (i.e. cycle 1A+1B=2x28=56 days) and at least until cycle 2 for patients in arm B (i.e. cycle 1A+1+2=28+14+14=56days, (b) one restaging acc. to RECIST 1.1 during study treatment. Unless (a) and (b) are unsatisfied due to early progression/death

Subject analysis set title	All patients treated
Subject analysis set type	Full analysis

Subject analysis set description:

All patients who have been treated with at least one dose of study medication (gemcitabine, erlotinib, FOLFIRINOX). One further patient was excluded from the Full Analysis due to later detected violation of inclusion- and exclusion criteria.

Reporting group values	Rash-positive (primary endpoint)	Patients - efficacy assessable	All patients treated
Number of subjects	90	123	144
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
median	63.0	63.0	63.5
full range (min-max)	24.0 to 75.0	24.0 to 75.0	24.0 to 75.0
Gender categorical Units: Subjects			
Female	32	47	57
Male	58	76	87
ECOG Performance Status Units: Subjects			
ECOG PS 0	64	78	87
ECOG PS 1	26	45	57

End points

End points reporting groups

Reporting group title	Run-in

Reporting group description:

Treatment with gemcitabine 1000 mg/^2 BSA weekly and erlotinib, 100 mg once daily for 4 weeks. Treatment was discontinued earlier in case of progression of the metastatic pancreatic adenocarcinoma, unacceptable toxicity or other reasons (patient's wish, investigator's decision).

Reporting group title	Arm A (rash-positve)

Reporting group description:

Patient who had developed skin rash after 4 weeks of treatment with gemcitabine 1000 mg/^2 BSA weekly and erlotinib 100 mg p.o. once daily in the Run-in phase (first 4 treatment weeks), continued treatment with gemcitabine 1000 mg/^2 weekly on D1, D7, D14 of each 28-day treatment cycle and erlotinib 100 mg p.o. once daily.
Treatment was continued until progression of the metastatic pancreatic adenocarcinoma, unacceptable toxicity or other reasons (patient's wish, investigator's decision).

Reporting group title	Arm B (rash-negative)

Reporting group description:

Patient who had developed no skin rash after 4 weeks of treatment with gemcitabine 1000 mg/^2 BSA weekly and erlotinib 100 mg p.o. once daily in the Run-in phase (first 4 treatment weeks), received further treatment with FOLFIRINOX (fluorouracil, folinic acid, irinotecan, oxaliplatin). Treatment was continued until progression of the metastatic pancreatic adenocarcinoma, unacceptable toxicity or other reasons (patient's wish, investigator's decision). Only rash-negative patients who were given FOLFIRINOX treatment after Run-in are included.

Subject analysis set title	Rash-positive (primary endpoint)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients, who are rash-positive after 4 weeks treatment with gemcitabine and erlotinib (all except one patient continued treatment with gemcitabine and erlotinib after the Run-in phase)

Subject analysis set title	Patients - efficacy assessable
Subject analysis set type	Per protocol

Subject analysis set description:

Patients of Full Analysis Set with: (a) at least two cycles for patients in arm A (i.e. cycle 1A+1B=2x28=56 days) and at least until cycle 2 for patients in arm B (i.e. cycle 1A+1+2=28+14+14=56days, (b) one restaging acc. to RECIST 1.1 during study treatment. Unless (a) and (b) are unsatisfied due to early progression/death

Subject analysis set title	All patients treated
Subject analysis set type	Full analysis

Subject analysis set description:

All patients who have been treated with at least one dose of study medication (gemcitabine, erlotinib, FOLFIRINOX). One further patient was excluded from the Full Analysis due to later detected violation of inclusion- and exclusion criteria.

Primary: 1-year survival rate in patients with skin rash

End point title	1-year survival rate in patients with skin rash[1]

End point description:

The primary endpoint is the 1-year survival rate for patients treated with gemcitabine + erlotinib developing skin rash of any grade during a four-week Run-in phase. Overall survival is calculated from the date of first adminstration of gemcitabine/erlotinib until date of death, censoring patients still alive with the date of last known contact (confirmatory analysis).

End point type	Primary

End point timeframe:

Survival status of each participating patient is recorded for at least 18 months after the date of enrollment.

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: The alternative hypothesis of a one-year-survival-rate of 40% was to be differed from the null hypothesis of 25% within a two-sided test (significance level 0.05, power 83%; pre-specified analysis). The alternative hypothesis and the null hypothesis are based on the publicated historical data in patients treated with gemcitabine/erlotinib in the PA.3 study (Moore 2007) and in patients treated with FOLFIRINOX (Conroy 2011), thus the statistical hypothetical test compared with historical groups.

End point values	Rash-positive (primary endpoint)			
Subject group type	Subject analysis set			
Number of subjects analysed	90			
Units: number of patients alive				
40.0% (29.8-50.9%)	36			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate (ORR)

End point title	Objective response rate (ORR)

End point description:

Percentage of patients who experienced "Complete response" or "Partial response" according to RECIST 1.1 (exploratory analysis)

End point type	Secondary

End point timeframe:

Evaluated every 8 weeks from the start of treatment until the end of treatment visit.

End point values	Arm B (rash-negative)	Rash-positive (primary endpoint)	Patients - efficacy assessable	All patients treated
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	27	90	123	144
Units: number of subjects with ORR				
33.3% (16.5 to 54.0%)	9	0	0	0
23.3% (15.1 to 33.4%)	0	21	0	0
24.4%	0	0	30	0
20.8%	0	0	0	30

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

End point title	Progression-free survival

End point description:

Progression-free survival is the time from the date of first administration of gemcitabin/erlotinib in Run-in until occurrence of progression or death of any cause. Patients without event will be censored with the last date known to be progression-free (exploratory analysis)

End point type	Secondary

End point timeframe:

Progression is evaluated every 8 weeks from the start of treatment until the end of treatment visit by means of imaging procedures. Survival status of each participating patient is recorded for at least 18 months after the date of enrollment.

End point values	Arm B (rash-negative)	Rash-positive (primary endpoint)	Patients - efficacy assessable	All patients treated
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	27	90	123	144
Units: Months				
arithmetic mean (confidence interval 95%)	6.6 (2.6 to 9.6)	3.8 (3.5 to 4.9)	3.6 (2.8 to 5.0)	3.6 (3.2 to 4.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall survival is calculated from the date of first application of gemcitabine/erlotinib until date of death, censoring patients still alive with the date of last known contact (exploratory analysis).

End point type	Secondary

End point timeframe:

Survival status of each participating patient is recorded for at least 18 months after the date of enrollment.

End point values	Arm B (rash-negative)	Rash-positive (primary endpoint)	Patients - efficacy assessable	All patients treated
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	27	90	123	144
Units: months				
median (confidence interval 95%)	10.9 (6.6 to 14.0)	10.1 (9.0 to 12.5)	10.0 (9.0 to 12.1)	9.7 (8.0 to 10.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Disease-control rate (DCR)

End point title	Disease-control rate (DCR)

End point description:

Percentage of patients who experienced "Complete response" or "Partial response" or "Stable disease" according to RECIST 1.1 (exploratory analysis)

End point type	Secondary

End point timeframe:

Evaluated every 8 weeks from the start of treatment until the end of treatment visit.

End point values	Arm B (rash-negative)	Rash-positive (primary endpoint)	Patients - efficacy assessable	All patients treated
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	27	90	123	144
Units: Number of patients with DCR				
63.0%	17	0	0	0
66.7%	0	60	0	0
61,0%	0	0	75	0
54,2%	0	0	0	78

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Date of signing informed consent until 28 days after last administration of study medication.

Adverse event reporting additional description:

Patients who received at least one adminstration of gemcitabine or erlotinib were analyzed as Safety Population. Only treatment-emergent events were analyzed.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Continued treatment with gemcitabin/erlotinib after Run-in

Reporting group description:

Rash-positive patients: Continued treatment with gemcitabine 100 mg/m^2 BSA weekly i.v. in Week 1-3 of each 28-day cycle and erlotinib 100 mg p.o. once daily after the Run-in phase until progression or unacceptable toxicity.
Only adverse events, experienced after Run-in during continued treatment with gemcitabine and erlotinib are taken into account.

Reporting group title	FOLFIRINOX after Run-in

Reporting group description:

Treatment with FOLFIRINOX after the Run-in phase:
Oxaliplatin 85 mg/m^2 on Day 1 of each 14-day cycle; i.v.
Folinic acid 400 mg/m^2 on Day 1 of each 14-day cycle; i.v.
Irinotecane 180 mg/m^2 on Day 1 of each 14-day cycle; i.v.
5-fluorouracil 400 mg/m² as bolus, followed by 2400 mg/m^2 as i.v. infusion over 46 hours
Treatment until progression or unacceptable toxicity.
Only adverse events, experienced after Run-in while receiving FOLFIRINOX treatment, are taken into account.

Reporting group title	Gemcitabine and erlotinib overall

Reporting group description:

Patients who were administered at least one dose of gemcitabine or erlotinib in the Run-in phase (first 4 treatment weeks; gemcitabine 1000 mg/^2 BSA weekly and erlotinib 100 mg p.o. once daily) and/or continued application of gemcitabine and erlotinib (gemcitabine 1000 mg/^2 BSA on D1, D7, D14 of a 28-day cycle and erlotinib 100 mg p.o. once daily until progression or unacceptable toxicity). Only adverse event in these treatment periods with treatment with gemcitabin and erlotinib are taken into account. Those adverse events, experienced after Run-in while receiving FOLFIRINOX treatment, are not taken into account.

Serious adverse events	Continued treatment with gemcitabin/erlotinib after Run-in	FOLFIRINOX after Run-in	Gemcitabine and erlotinib overall
Total subjects affected by serious adverse events			
subjects affected / exposed	42 / 89 (47.19%)	15 / 28 (53.57%)	70 / 145 (48.28%)
number of deaths (all causes)	9	2	16
number of deaths resulting from adverse events	0	1	9
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour associated fever			

subjects affected / exposed	1 / 89 (1.12%)	0 / 28 (0.00%)	1 / 145 (0.69%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 89 (0.00%)	0 / 28 (0.00%)	1 / 145 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism			
subjects affected / exposed	0 / 89 (0.00%)	0 / 28 (0.00%)	1 / 145 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 89 (1.12%)	0 / 28 (0.00%)	1 / 145 (0.69%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis	Additional description: The pre-printed term was ""Thromboembolic events". Thus, the terms thrombosis, pulmonary embolism and jugular vein thrombosis are summarized under "Thrombosis".		
subjects affected / exposed	5 / 89 (5.62%)	1 / 28 (3.57%)	6 / 145 (4.14%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Medical device implantation			
subjects affected / exposed	1 / 89 (1.12%)	0 / 28 (0.00%)	1 / 145 (0.69%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Catheter site haematoma			
subjects affected / exposed	1 / 89 (1.12%)	0 / 28 (0.00%)	1 / 145 (0.69%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			

subjects affected / exposed	2 / 89 (2.25%)	0 / 28 (0.00%)	2 / 145 (1.38%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device dislocation			
subjects affected / exposed	0 / 89 (0.00%)	0 / 28 (0.00%)	1 / 145 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device occlusion			
subjects affected / exposed	2 / 89 (2.25%)	0 / 28 (0.00%)	2 / 145 (1.38%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	5 / 89 (5.62%)	2 / 28 (7.14%)	6 / 145 (4.14%)
occurrences causally related to treatment / all	1 / 6	1 / 2	2 / 7
deaths causally related to treatment / all	0 / 1	1 / 1	0 / 1
Impaired healing			
subjects affected / exposed	1 / 89 (1.12%)	0 / 28 (0.00%)	1 / 145 (0.69%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	1 / 89 (1.12%)	0 / 28 (0.00%)	2 / 145 (1.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain	Additional description: Summarized pre-printed term "Pain" comprising summarized terms "Abdominal pain, back pain, chest pain, abdominal pain upper".		
subjects affected / exposed	5 / 89 (5.62%)	2 / 28 (7.14%)	9 / 145 (6.21%)
occurrences causally related to treatment / all	0 / 6	0 / 2	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	3 / 89 (3.37%)	1 / 28 (3.57%)	5 / 145 (3.45%)
occurrences causally related to treatment / all	0 / 3	1 / 1	2 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			

Pneumonitis	Additional description: Summarized terms "Pneumonitis" and "Interstitial lung disease".		
subjects affected / exposed	1 / 89 (1.12%)	0 / 28 (0.00%)	1 / 145 (0.69%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 89 (0.00%)	1 / 28 (3.57%)	1 / 145 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 89 (0.00%)	0 / 28 (0.00%)	1 / 145 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood uric acid increased			
subjects affected / exposed	1 / 89 (1.12%)	0 / 28 (0.00%)	1 / 145 (0.69%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
C-reactive protein increased			
subjects affected / exposed	2 / 89 (2.25%)	0 / 28 (0.00%)	2 / 145 (1.38%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	1 / 89 (1.12%)	0 / 28 (0.00%)	1 / 145 (0.69%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 89 (2.25%)	0 / 28 (0.00%)	5 / 145 (3.45%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased	Additional description: Terms "Blood bilirubin increased" and "jaundice"		
subjects affected / exposed	1 / 89 (1.12%)	0 / 28 (0.00%)	5 / 145 (3.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Weight decreased	Additional description: Terms "Cachexia" and "Weight decreased"		
subjects affected / exposed	0 / 89 (0.00%)	1 / 28 (3.57%)	0 / 145 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Anastomotic complication			
subjects affected / exposed	0 / 89 (0.00%)	0 / 28 (0.00%)	1 / 145 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	0 / 89 (0.00%)	1 / 28 (3.57%)	0 / 145 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 89 (1.12%)	0 / 28 (0.00%)	1 / 145 (0.69%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Nervous system disorders			
Cerebrovascular accident	Additional description: Summarized terms "Cerebrovascular accident" and "Cerebral infarction"		
subjects affected / exposed	1 / 89 (1.12%)	1 / 28 (3.57%)	2 / 145 (1.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	0 / 89 (0.00%)	0 / 28 (0.00%)	1 / 145 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 89 (1.12%)	1 / 28 (3.57%)	2 / 145 (1.38%)
occurrences causally related to treatment / all	1 / 1	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			

subjects affected / exposed	1 / 89 (1.12%)	1 / 28 (3.57%)	1 / 145 (0.69%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukocytosis			
subjects affected / exposed	1 / 89 (1.12%)	0 / 28 (0.00%)	1 / 145 (0.69%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Optic ischaemic neuropathy			
subjects affected / exposed	1 / 89 (1.12%)	0 / 28 (0.00%)	1 / 145 (0.69%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 89 (0.00%)	1 / 28 (3.57%)	1 / 145 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	1 / 89 (1.12%)	0 / 28 (0.00%)	1 / 145 (0.69%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 89 (0.00%)	1 / 28 (3.57%)	1 / 145 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Ileus			
subjects affected / exposed	1 / 89 (1.12%)	0 / 28 (0.00%)	2 / 145 (1.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	1 / 89 (1.12%)	0 / 28 (0.00%)	1 / 145 (0.69%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Nausea			

subjects affected / exposed	2 / 89 (2.25%)	2 / 28 (7.14%)	4 / 145 (2.76%)
occurrences causally related to treatment / all	1 / 3	2 / 2	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	3 / 89 (3.37%)	2 / 28 (7.14%)	5 / 145 (3.45%)
occurrences causally related to treatment / all	1 / 4	2 / 2	1 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	1 / 89 (1.12%)	0 / 28 (0.00%)	1 / 145 (0.69%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 89 (1.12%)	0 / 28 (0.00%)	1 / 145 (0.69%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 89 (0.00%)	0 / 28 (0.00%)	1 / 145 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Duodenitis			
subjects affected / exposed	0 / 89 (0.00%)	1 / 28 (3.57%)	0 / 145 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	1 / 89 (1.12%)	0 / 28 (0.00%)	1 / 145 (0.69%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Bile duct stenosis			
subjects affected / exposed	3 / 89 (3.37%)	0 / 28 (0.00%)	3 / 145 (2.07%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			

subjects affected / exposed	0 / 89 (0.00%)	0 / 28 (0.00%)	1 / 145 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholestasis			
subjects affected / exposed	2 / 89 (2.25%)	0 / 28 (0.00%)	5 / 145 (3.45%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	0 / 89 (0.00%)	0 / 28 (0.00%)	1 / 145 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Perforation bile duct			
subjects affected / exposed	0 / 89 (0.00%)	0 / 28 (0.00%)	1 / 145 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 89 (1.12%)	0 / 28 (0.00%)	1 / 145 (0.69%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 89 (1.12%)	0 / 28 (0.00%)	1 / 145 (0.69%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 89 (1.12%)	0 / 28 (0.00%)	1 / 145 (0.69%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection	Additional description: The pre-printed term was infection without further differentiation. The term infection comprises among others also the terms "Cholangitis", "Peritonitis bacterial", "Atypical pneumonia".		
subjects affected / exposed	16 / 89 (17.98%)	3 / 28 (10.71%)	22 / 145 (15.17%)
occurrences causally related to treatment / all	1 / 16	1 / 4	2 / 22
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Sepsis			
subjects affected / exposed	1 / 89 (1.12%)	0 / 28 (0.00%)	1 / 145 (0.69%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 89 (0.00%)	2 / 28 (7.14%)	0 / 145 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Continued treatment with gemcitabin/erlotinib after Run-in	FOLFIRINOX after Run-in	Gemcitabine and erlotinib overall
Total subjects affected by non-serious adverse events			
subjects affected / exposed	89 / 89 (100.00%)	28 / 28 (100.00%)	145 / 145 (100.00%)
Investigations			
Weight decreased			
subjects affected / exposed	26 / 89 (29.21%)	13 / 28 (46.43%)	37 / 145 (25.52%)
occurrences (all)	30	18	45
Blood bilirubin increased			
subjects affected / exposed	31 / 89 (34.83%)	4 / 28 (14.29%)	51 / 145 (35.17%)
occurrences (all)	33	4	54
Blood alkaline phosphatase increased			
subjects affected / exposed	26 / 89 (29.21%)	9 / 28 (32.14%)	38 / 145 (26.21%)
occurrences (all)	28	11	40
Blood lactate dehydrogenase increased			
subjects affected / exposed	12 / 89 (13.48%)	2 / 28 (7.14%)	15 / 145 (10.34%)
occurrences (all)	15	2	18
C-reactive protein increased			
subjects affected / exposed	18 / 89 (20.22%)	6 / 28 (21.43%)	25 / 145 (17.24%)
occurrences (all)	22	8	30
Blood creatinine increased			
subjects affected / exposed	21 / 89 (23.60%)	4 / 28 (14.29%)	28 / 145 (19.31%)
occurrences (all)	26	16	33

Gamma-glutamyltransferase increased	Additional description: Terms "Gamma-glutamyltransferase" and "Gamma-glutamyltransferase increased"		
subjects affected / exposed	52 / 89 (58.43%)	21 / 28 (75.00%)	79 / 145 (54.48%)
occurrences (all)	60	27	89
Protein total decreased			
subjects affected / exposed	7 / 89 (7.87%)	5 / 28 (17.86%)	10 / 145 (6.90%)
occurrences (all)	7	6	12
Aspartate aminotransferase increased			
subjects affected / exposed	21 / 89 (23.60%)	4 / 28 (14.29%)	30 / 145 (20.69%)
occurrences (all)	21	6	32
Hepatic enzyme increased	Additional description: Summarized pre-printed term "Liver values increased (ALT)" and term "Hepatic enzyme increased" and term "Transaminases" and term "Alanine aminotransferase increased".		
subjects affected / exposed	79 / 89 (88.76%)	20 / 28 (71.43%)	117 / 145 (80.69%)
occurrences (all)	98	27	140
Blood urea increased			
subjects affected / exposed	5 / 89 (5.62%)	1 / 28 (3.57%)	5 / 145 (3.45%)
occurrences (all)	6	4	6
Vascular disorders			
Hypertension	Additional description: Summarized terms "Hypertension" and "Blood pressure increased".		
subjects affected / exposed	8 / 89 (8.99%)	3 / 28 (10.71%)	11 / 145 (7.59%)
occurrences (all)	9	3	13
Thrombosis	Additional description: The pre-printed term was ""Thromboembolic events". Thus, the terms thrombosis, pulmonary embolism and jugular vein thrombosis are summarized under "Thrombosis".		
subjects affected / exposed	8 / 89 (8.99%)	4 / 28 (14.29%)	11 / 145 (7.59%)
occurrences (all)	10	4	13
Nervous system disorders			
Dizziness			
subjects affected / exposed	10 / 89 (11.24%)	4 / 28 (14.29%)	15 / 145 (10.34%)
occurrences (all)	11	4	16
Dysgeusia			
subjects affected / exposed	7 / 89 (7.87%)	3 / 28 (10.71%)	13 / 145 (8.97%)
occurrences (all)	8	5	14
Peripheral sensory neuropathy			
subjects affected / exposed	13 / 89 (14.61%)	16 / 28 (57.14%)	18 / 145 (12.41%)
occurrences (all)	13	35	18
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	87 / 89 (97.75%)	25 / 28 (89.29%)	135 / 145 (93.10%)
occurrences (all)	90	33	143
Leukopenia			
subjects affected / exposed	63 / 89 (70.79%)	10 / 28 (35.71%)	98 / 145 (67.59%)
occurrences (all)	88	22	130
Neutropenia			
subjects affected / exposed	26 / 89 (29.21%)	7 / 28 (25.00%)	38 / 145 (26.21%)
occurrences (all)	31	18	46
Lymphopenia	Additional description: Summarized terms "Lymphopenia" and "Lymphocyte count decreased".		
subjects affected / exposed	9 / 89 (10.11%)	4 / 28 (14.29%)	13 / 145 (8.97%)
occurrences (all)	11	4	15
Thrombocytopenia			
subjects affected / exposed	51 / 89 (57.30%)	14 / 28 (50.00%)	96 / 145 (66.21%)
occurrences (all)	65	22	125
Thrombocytosis			
subjects affected / exposed	6 / 89 (6.74%)	5 / 28 (17.86%)	8 / 145 (5.52%)
occurrences (all)	6	6	8
General disorders and administration site conditions			
Chills			
subjects affected / exposed	6 / 89 (6.74%)	0 / 28 (0.00%)	9 / 145 (6.21%)
occurrences (all)	6	0	9
Fatigue			
subjects affected / exposed	48 / 89 (53.93%)	19 / 28 (67.86%)	89 / 145 (61.38%)
occurrences (all)	55	43	97
Feeling cold			
subjects affected / exposed	3 / 89 (3.37%)	2 / 28 (7.14%)	3 / 145 (2.07%)
occurrences (all)	4	2	4
General physical health deterioration			
subjects affected / exposed	4 / 89 (4.49%)	3 / 28 (10.71%)	10 / 145 (6.90%)
occurrences (all)	5	3	11
Oedema peripheral	Additional description: Terms "Oedema peripheral" and "Oedema lower leg"		
subjects affected / exposed	26 / 89 (29.21%)	8 / 28 (28.57%)	40 / 145 (27.59%)
occurrences (all)	39	10	47
Pain	Additional description: Summarized pre-printed term "Pain" comprising summarized terms "Abdominal pain, back pain, chest pain, abdominal pain upper" et others.		

subjects affected / exposed	54 / 89 (60.67%)	23 / 28 (82.14%)	104 / 145 (71.72%)
occurrences (all)	67	34	123
Pyrexia			
subjects affected / exposed	16 / 89 (17.98%)	3 / 28 (10.71%)	27 / 145 (18.62%)
occurrences (all)	20	3	32
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	23 / 89 (25.84%)	6 / 28 (21.43%)	35 / 145 (24.14%)
occurrences (all)	29	15	42
Diarrhoea			
subjects affected / exposed	30 / 89 (33.71%)	13 / 28 (46.43%)	59 / 145 (40.69%)
occurrences (all)	35	23	69
Ascites			
subjects affected / exposed	6 / 89 (6.74%)	1 / 28 (3.57%)	7 / 145 (4.83%)
occurrences (all)	7	1	8
Dry mouth			
subjects affected / exposed	4 / 89 (4.49%)	2 / 28 (7.14%)	8 / 145 (5.52%)
occurrences (all)	4	2	8
Dyspepsia			
subjects affected / exposed	6 / 89 (6.74%)	2 / 28 (7.14%)	8 / 145 (5.52%)
occurrences (all)	7	3	10
Stomatitis	Additional description: The term "Stomatitis" comprises stomatitis and mucositis at another site.		
subjects affected / exposed	14 / 89 (15.73%)	8 / 28 (28.57%)	26 / 145 (17.93%)
occurrences (all)	15	19	27
Nausea			
subjects affected / exposed	49 / 89 (55.06%)	23 / 28 (82.14%)	82 / 145 (56.55%)
occurrences (all)	59	43	96
Vomiting			
subjects affected / exposed	21 / 89 (23.60%)	13 / 28 (46.43%)	36 / 145 (24.83%)
occurrences (all)	23	16	43
Flatulence			
subjects affected / exposed	5 / 89 (5.62%)	0 / 28 (0.00%)	5 / 145 (3.45%)
occurrences (all)	5	0	5
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	6 / 89 (6.74%)	2 / 28 (7.14%)	6 / 145 (4.14%)
occurrences (all)	6	2	6
Dyspnoea			
subjects affected / exposed	14 / 89 (15.73%)	5 / 28 (17.86%)	17 / 145 (11.72%)
occurrences (all)	17	5	20
Epistaxis			
subjects affected / exposed	5 / 89 (5.62%)	0 / 28 (0.00%)	7 / 145 (4.83%)
occurrences (all)	5	0	9
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	22 / 89 (24.72%)	10 / 28 (35.71%)	25 / 145 (17.24%)
occurrences (all)	23	20	27
Dry skin			
subjects affected / exposed	13 / 89 (14.61%)	5 / 28 (17.86%)	19 / 145 (13.10%)
occurrences (all)	16	10	23
Night sweats			
subjects affected / exposed	4 / 89 (4.49%)	1 / 28 (3.57%)	8 / 145 (5.52%)
occurrences (all)	4	1	8
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	5 / 89 (5.62%)	4 / 28 (14.29%)	6 / 145 (4.14%)
occurrences (all)	6	7	7
Pruritus			
subjects affected / exposed	10 / 89 (11.24%)	2 / 28 (7.14%)	21 / 145 (14.48%)
occurrences (all)	11	2	22
Rash			
subjects affected / exposed	15 / 89 (16.85%)	3 / 28 (10.71%)	17 / 145 (11.72%)
occurrences (all)	19	3	23
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 89 (2.25%)	2 / 28 (7.14%)	2 / 145 (1.38%)
occurrences (all)	2	3	2
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	6 / 89 (6.74%)	0 / 28 (0.00%)	6 / 145 (4.14%)
occurrences (all)	8	0	8

Infections and infestations			
Infection	Additional description: The pre-printed term was infection without further differentiation. The term "Infection" comprises among others also the terms "Cholangitis", "Peritonitis bacterial", "Atypical pneumonia".		
subjects affected / exposed	21 / 89 (23.60%)	3 / 28 (10.71%)	35 / 145 (24.14%)
occurrences (all)	24	3	38
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	31 / 89 (34.83%)	6 / 28 (21.43%)	47 / 145 (32.41%)
occurrences (all)	38	11	56
Hypokalaemia	Additional description: Summarized terms "Hypokalaemia" and "Blood potassium decreased".		
subjects affected / exposed	5 / 89 (5.62%)	6 / 28 (21.43%)	12 / 145 (8.28%)
occurrences (all)	6	12	14
Hyperglycaemia	Additional description: Summarized terms "Hyperglycaemia" and "Blood glucose increased".		
subjects affected / exposed	2 / 89 (2.25%)	3 / 28 (10.71%)	5 / 145 (3.45%)
occurrences (all)	2	4	5
Hyponatraemia	Additional description: Summarized terms "Hyponatraemia" and "Blood sodium decreased".		
subjects affected / exposed	7 / 89 (7.87%)	6 / 28 (21.43%)	9 / 145 (6.21%)
occurrences (all)	8	6	9
Hypocalcaemia			
subjects affected / exposed	2 / 89 (2.25%)	2 / 28 (7.14%)	3 / 145 (2.07%)
occurrences (all)	3	3	4
Hypoalbuminaemia	Additional description: Summarized terms "Hypoalbuminaemia" and "Blood albumin decreased".		
subjects affected / exposed	12 / 89 (13.48%)	3 / 28 (10.71%)	14 / 145 (9.66%)
occurrences (all)	13	7	16

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported