Clinical trial results:
Prospective Randomized Multicenter Phase II Trial to Investigate Intensified Neoadjuvant Chemotherapy in Locally Advanced Pancreatic Cancer

Summary

EudraCT number	2013-004796-12
Trial protocol	DE
Global end of trial date	19 February 2020

Results information

Result version number	v1 (current)
This version publication date	30 April 2022
First version publication date	30 April 2022

Trial information

Trial identification

Sponsor protocol code	AIO-PAK-0113

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02125136
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AIO-Studien-gGmbH
Sponsor organisation address	Kuno-Fischer-Str. 8, Berlin, Germany, 14057
Public contact	AIO-Studien-gGmbH, AIO-Studien-gGmbH, 0049 30322932931, info@aio-studien-ggmbh.de
Scientific contact	AIO-Studien-gGmbH, AIO-Studien-gGmbH, 0049 30322932931, info@aio-studien-ggmbh.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	01 December 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 February 2020
Global end of trial reached?	Yes
Global end of trial date	19 February 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effect of intensified neoadjuvant chemotherapy on conversion rate to resetcability in LAPC.

Protection of trial subjects:

This study was planned, analyzed and conducted according to the study protocol and in accordance with the International Conference on Harmonization (ICH) ‚Guideline for Good Clinical Practice E6(R1)‘, CPMP/ICH/135/95, based on the principles of the Declaration of Helsinki (1964) and its October 1996 amendment (Somerset West, South Africa). The study was duly conducted in compliance with the German Arzneimittelgesetz (AMG; German Drug Law), and the corresponding Directive 2001/20/EC. Subjects were fully informed regarding all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 November 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 168
Worldwide total number of subjects	168
EEA total number of subjects	168

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)	99
From 65 to 84 years	69

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The recruitment period of this clinical trial lasted from 18 November 2014 (first patient registered) to 27 April 2018 (last patient registered). Patients were recruited to 28 trial centres in Germany.

Pre-assignment

Screening details:

A total of 168 patients were screened for the clinical trial, 165 of whom received at least one dose of non-randomized neoadjuvant induction therapy.

Period 1

Period 1 title	Non-randomized induction
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	nab-Pac/Gem induction treatment (non-randomized)

Arm description:

Prior to randomization, all study participants received two cycles of induction treatment with nab-paclitaxel and gemcitabine.

Arm type	SoC induction treatment
Investigational medicinal product name	nab-Paclitaxel
Investigational medicinal product code	
Other name	Abraxane
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received 125 mg/m^2 on days 1, 8, and 15 of a 28-day cycle as intravenous infusion over 30 minutes.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine was administered at a dose of 1000 mg/m^2 on days 1, 8, and 15 of a 28-day cycle as intravenous infusion over a period of 30 minutes.

Number of subjects in period 1	nab-Pac/Gem induction treatment (non-randomized)
Started	168
Completed	130
Not completed	38
Consent withdrawn by subject	3
Patient's wish	3
Adverse event	4

Progressive disease	22
Protocol deviation	5
not specified	1

Period 2

Period 2 title	Randomized treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A - nab-Pac/Gem

Arm description:

Patients randomized to Arm A received two additional cycles of induction treatment with nab-paclitaxel and gemcitabine. Cycle length of 28 days was maintained.

Arm type	Active comparator
Investigational medicinal product name	nab-paclitaxel
Investigational medicinal product code	
Other name	Abraxane
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received 125 mg/m^2 on days 1, 8, and 15 of a 28-day cycle as intravenous infusion over 30 minutes.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine was administered at a dose of 1000 mg/m^2 on days 1, 8, and 15 of a 28-day cycle as intravenous infusion over a period of 30 minutes.

Arm title	Arm B - FOLFIRINOX

Arm description:

Patients randomized to Arm B switched their induction treatment after two cycles of nab-paclitaxel plus gemcitabine to FOLFIRINOX. The latter was administered for four cycles of 14 days.

66 patients were randomized to Arm B. Of these, 61 received randomized treatment.

Arm type	Experimental
Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Oxaliplatin was given at 85 mg/m^2 as a 2-hour i.v. infusion.

Investigational medicinal product name	Folinic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Folinic acid was given at 400 mg/m^2 as a 2-hour i.v. infusion.

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

Dosage and administration details:

Irinotecan was given at 180 mg/m^2 as a 90-minute i.v. infusion (application through a Y-connector parallel to infusion of folinic acid and 30 minutes after start of folinic acid was possible).

Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5-Fluorouracil 400 mg/m^2 was administered as i.v. bolus, followed by a continuous i.v. infusion of fluorouracil at 2400 mg/m^2 over 46 hours starting on Day 1.

Number of subjects in period 2	Arm A - nab-Pac/Gem	Arm B - FOLFIRINOX
Started	64	66
Neoadjuvant chemotherapy	60	51
Explorative laparotomy	40	42
Resection in curative intent	23	29
Adjuvant chemotherapy	16	21
Completed	12	18
Not completed	52	48
Physician decision	9	5
Screening failure	-	1
Consent withdrawn/patient's wish	9	11
Death	1	1
Other	1	-
Adverse event	6	10
Suspected progression	-	1
Progressive disease	10	6
No resectability/no resection	15	13
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Non-randomized induction
Reporting group description:	
This reporting group contains all enrolled patients. All but 3 of these received non-randomized induction treatment.	

Reporting group values	Non-randomized induction	Total	
Number of subjects	168	168	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	99	99	
85 years and over	69	69	
Gender categorical Units: Subjects			
Female	81	81	
Male	87	87	

End points

End points reporting groups

Reporting group title	nab-Pac/Gem induction treatment (non-randomized)

Reporting group description:

Prior to randomization, all study participants received two cycles of induction treatment with nab-paclitaxel and gemcitabine.

Reporting group title	Arm A - nab-Pac/Gem

Reporting group description:

Patients randomized to Arm A received two additional cycles of induction treatment with nab-paclitaxel and gemcitabine. Cycle length of 28 days was maintained.

Reporting group title	Arm B - FOLFIRINOX

Reporting group description:

Patients randomized to Arm B switched their induction treatment after two cycles of nab-paclitaxel plus gemcitabine to FOLFIRINOX. The latter was administered for four cycles of 14 days.

66 patients were randomized to Arm B. Of these, 61 received randomized treatment.

Subject analysis set title	EFF-res
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The EFF analysis set contains all subjects who received at least one dose of randomized study treatment. The EFF-res set contains all subjects of the EFF set who underwent tumor resection.

Primary: Resection rate

End point title	Resection rate

End point description:

End point type	Primary

End point timeframe:

The primary endpoint was the rate of patients who underwent pancreatic resection in curative intention based on the evaluation during exploratory laparotomy after intensified neoadjuvant chemotherapy.

End point values	Arm A - nab-Pac/Gem	Arm B - FOLFIRINOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	66		
Units: Resected patients	23	29		

Statistical analyses

Statistical analysis title	Resection rate

Statistical analysis description:

With regard to the conversion to resectability, patients in whom (after randomization) resectability with curative intent was not achieved were evaluated as unresectable.

Comparison groups	Arm B - FOLFIRINOX v Arm A - nab-Pac/Gem

Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3757
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	0.716
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.354
upper limit	1.448

Secondary: Progression-free survival

End point title	Progression-free survival

End point description:

For each patient who was not known to have had a progression or death as of the data extract date, the PFS time was censored at the date of the patient's last recorded study visit or follow-up. Patients were observed for a median duration of 13.8 months (mean 16.0 ± 10.9 months, minimum 0.3, maximum 55.2 months).

End point type	Secondary

End point timeframe:

Progression-free survival (PFS) is the time from the first day of the first cycle of neoadjuvant chemotherapy to the date of objective disease progression or to death of any cause.

End point values	Arm A - nab-Pac/Gem	Arm B - FOLFIRINOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	66		
Units: months				
number (confidence interval 95%)	10.2 (8.4 to 11.8)	12.3 (9.6 to 13.8)		

Statistical analyses

Statistical analysis title	Progression-free survival
Comparison groups	Arm A - nab-Pac/Gem v Arm B - FOLFIRINOX
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.145
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.745

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.501
upper limit	1.109

Secondary: Relapse-free survival

End point title	Relapse-free survival

End point description:

For each patient who was not known to have had a relapse as of the data extract cut-off date, the time to relapse was censored at the date of the patient's last recorded study visit or follow-up.

End point type	Secondary

End point timeframe:

Relapse-free survival (RFS) is the time from the first day after pancreatic resection to the date of relapse, defined as either local relapse of pancreatic cancer or occurrence of distant metastases, during or after adjuvant chemotherapy.

End point values	Arm A - nab-Pac/Gem	Arm B - FOLFIRINOX	EFF-res	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	23	29	52	
Units: months				
median (confidence interval 95%)	7.4 (5.9 to 12.2)	9.9 (7.9 to 10.8)	8.2 (7.4 to 10.6)	

Statistical analyses

Statistical analysis title	Relapse-free survival
Comparison groups	Arm B - FOLFIRINOX v Arm A - nab-Pac/Gem
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.696
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.883
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.473
upper limit	1.696

Secondary: Objective response rate

End point title	Objective response rate

End point description:

Restaging 2 was performed at the end of randomized neoadjuvant chemotherapy treatment: Cycle 2 Day 24± 3 days for nab-Pac/Gem or Cycle 4 Day 10 ± 3 days for FOLFIRINOX.

End point type	Secondary

End point timeframe:

The objective response rate (ORR) is defined as the rate of patients achieving partial response (PR) or complete response (CR) according to RECIST version 1.1 criteria at restaging 2.

End point values	Arm A - nab-Pac/Gem	Arm B - FOLFIRINOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	66		
Units: Number of patients with CR or PR	14	11		

Statistical analyses

Statistical analysis title	Objective response rate
Comparison groups	Arm B - FOLFIRINOX v Arm A - nab-Pac/Gem
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5087
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.582
upper limit	3.367

Secondary: Disease control rate

End point title	Disease control rate

End point description:

Restaging 2 was performed at the end of randomized neoadjuvant chemotherapy treatment: Cycle 2 Day 24± 3 days for nab-Pac/Gem or Cycle 4 Day 10 ± 3 days for FOLFIRINOX.

End point type	Secondary

End point timeframe:

The disease control rate (DCR) is defined as the rate of patients achieving partial response (PR) or complete response (CR) according to RECIST version 1.1 criteria at restaging 2.

End point values	Arm A - nab-Pac/Gem	Arm B - FOLFIRINOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	66		
Units: Patients with CR, PR or SD	52	47		

Statistical analyses

Statistical analysis title	Disease control rate
Comparison groups	Arm A - nab-Pac/Gem v Arm B - FOLFIRINOX
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2187
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	1.752
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.769
upper limit	3.991

Secondary: Rate of R0/R1 resection according to CRM concept

End point title	Rate of R0/R1 resection according to CRM concept

End point description:

End point type	Secondary

End point timeframe:

Rates of R0/R1 resections according to the circumferential resection margin (CRM) concept

End point values	Arm A - nab-Pac/Gem	Arm B - FOLFIRINOX	EFF-res	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	23	29	52	
Units: Resected patients				
R0 wide	6	13	19	
R0 narrow	10	7	17	
R0	1	0	1	
R1	6	9	15	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

For each patient for whom it was not known whether he/she was still alive at the data extract date, the time to death of any cause was censored at the date of the patient's last recorded study visit or follow-up.

End point type	Secondary

End point timeframe:

Overall survival (OS) is the time from the first day of the first cycle of neoadjuvant chemotherapy to the date of death of any cause.

End point values	Arm A - nab-Pac/Gem	Arm B - FOLFIRINOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	66		
Units: months				
median (confidence interval 95%)	18.8 (16.0 to 22.2)	20.7 (13.8 to 27.4)		

Statistical analyses

Statistical analysis title	Overall survival
Comparison groups	Arm A - nab-Pac/Gem v Arm B - FOLFIRINOX
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6213
Method	Logrank

Adverse events

Adverse events information

Timeframe for reporting adverse events:

from first administration of any IMP to 28 days after the last dose of any IMP. The time interval from date of exploratory laparotomy / pancreatic resection until 14 days before first administration of adjuvant chemotherapy was excluded from reporting.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Pts. with non-randomized induction treatment only

Reporting group description:

This group reports on patients who received only non-randomized induction treatment with nab-paclitaxel/gemcitabine and did not proceed to the randomized phase of induction treatment.

Reporting group title	Treatment Arm A

Reporting group description: -

Reporting group title	Treatment Arm B

Reporting group description: -

Serious adverse events	Pts. with non-randomized induction treatment only	Treatment Arm A	Treatment Arm B
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 35 (68.57%)	28 / 64 (43.75%)	33 / 66 (50.00%)
number of deaths (all causes)	0	1	2
number of deaths resulting from adverse events	0	1	2
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 35 (0.00%)	1 / 64 (1.56%)	0 / 66 (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
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 35 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
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 related thrombosis			

subjects affected / exposed	0 / 35 (0.00%)	1 / 64 (1.56%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 35 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 35 (0.00%)	2 / 64 (3.13%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucosal inflammation			
subjects affected / exposed	0 / 35 (0.00%)	1 / 64 (1.56%)	0 / 66 (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
Pyrexia			
subjects affected / exposed	1 / 35 (2.86%)	1 / 64 (1.56%)	4 / 66 (6.06%)
occurrences causally related to treatment / all	2 / 2	0 / 1	2 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	0 / 35 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	0 / 35 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 35 (0.00%)	0 / 64 (0.00%)	2 / 66 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pulmonary embolism			
subjects affected / exposed	0 / 35 (0.00%)	1 / 64 (1.56%)	0 / 66 (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
Psychiatric disorders			
Psychotic disorder			
subjects affected / exposed	1 / 35 (2.86%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device dislocation			
subjects affected / exposed	0 / 35 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
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	1 / 35 (2.86%)	3 / 64 (4.69%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 35 (2.86%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia paroxysmal			
subjects affected / exposed	1 / 35 (2.86%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 35 (0.00%)	1 / 64 (1.56%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Complex regional pain syndrome			

subjects affected / exposed	1 / 35 (2.86%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 35 (0.00%)	1 / 64 (1.56%)	0 / 66 (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
Thalamic infarction			
subjects affected / exposed	0 / 35 (0.00%)	1 / 64 (1.56%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical haemolytic uraemic syndrome			
subjects affected / exposed	0 / 35 (0.00%)	1 / 64 (1.56%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Amaurosis fugax			
subjects affected / exposed	0 / 35 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 35 (8.57%)	1 / 64 (1.56%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	1 / 35 (2.86%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	2 / 35 (5.71%)	1 / 64 (1.56%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 35 (0.00%)	2 / 64 (3.13%)	2 / 66 (3.03%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecaloma			
subjects affected / exposed	1 / 35 (2.86%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer perforation			
subjects affected / exposed	0 / 35 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired gastric emptying			
subjects affected / exposed	1 / 35 (2.86%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			

subjects affected / exposed	2 / 35 (5.71%)	1 / 64 (1.56%)	5 / 66 (7.58%)
occurrences causally related to treatment / all	0 / 2	1 / 1	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 35 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 35 (2.86%)	1 / 64 (1.56%)	4 / 66 (6.06%)
occurrences causally related to treatment / all	0 / 1	1 / 1	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	6 / 35 (17.14%)	6 / 64 (9.38%)	8 / 66 (12.12%)
occurrences causally related to treatment / all	0 / 7	1 / 8	4 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis infective			
subjects affected / exposed	1 / 35 (2.86%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholestasis			
subjects affected / exposed	4 / 35 (11.43%)	4 / 64 (6.25%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device occlusion			

subjects affected / exposed	0 / 35 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	0 / 35 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 35 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 35 (0.00%)	1 / 64 (1.56%)	0 / 66 (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
Prerenal failure			
subjects affected / exposed	0 / 35 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	0 / 35 (0.00%)	1 / 64 (1.56%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal infection			
subjects affected / exposed	0 / 35 (0.00%)	1 / 64 (1.56%)	0 / 66 (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
Bacterial infection			
subjects affected / exposed	1 / 35 (2.86%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cystitis			
subjects affected / exposed	1 / 35 (2.86%)	1 / 64 (1.56%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 35 (0.00%)	1 / 64 (1.56%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 35 (0.00%)	1 / 64 (1.56%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epididymitis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 35 (0.00%)	2 / 64 (3.13%)	2 / 66 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile infection			
subjects affected / exposed	1 / 35 (2.86%)	2 / 64 (3.13%)	2 / 66 (3.03%)
occurrences causally related to treatment / all	1 / 1	2 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	1 / 35 (2.86%)	2 / 64 (3.13%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	1 / 1	1 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver abscess			
subjects affected / exposed	0 / 35 (0.00%)	2 / 64 (3.13%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic infection			

subjects affected / exposed	0 / 35 (0.00%)	1 / 64 (1.56%)	0 / 66 (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
Peritonitis bacterial			
subjects affected / exposed	1 / 35 (2.86%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	0 / 35 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 35 (0.00%)	1 / 64 (1.56%)	0 / 66 (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
Wound sepsis			
subjects affected / exposed	0 / 35 (0.00%)	1 / 64 (1.56%)	0 / 66 (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
Body temperature increased			
subjects affected / exposed	0 / 35 (0.00%)	1 / 64 (1.56%)	0 / 66 (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
C-reactive protein increased			
subjects affected / exposed	1 / 35 (2.86%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			

subjects affected / exposed	0 / 35 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	0 / 35 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 35 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	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	Pts. with non-randomized induction treatment only	Treatment Arm A	Treatment Arm B
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 35 (97.14%)	64 / 64 (100.00%)	61 / 66 (92.42%)
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	3 / 35 (8.57%)	3 / 64 (4.69%)	8 / 66 (12.12%)
occurrences (all)	3	7	13
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 35 (8.57%)	2 / 64 (3.13%)	7 / 66 (10.61%)
occurrences (all)	3	3	11
C-reactive protein increased			
subjects affected / exposed	1 / 35 (2.86%)	3 / 64 (4.69%)	4 / 66 (6.06%)
occurrences (all)	1	3	5
Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 35 (8.57%)	5 / 64 (7.81%)	6 / 66 (9.09%)
occurrences (all)	3	5	7
Neutrophil count decreased			
subjects affected / exposed	1 / 35 (2.86%)	7 / 64 (10.94%)	9 / 66 (13.64%)
occurrences (all)	1	16	16
Platelet count decreased			
subjects affected / exposed	3 / 35 (8.57%)	4 / 64 (6.25%)	5 / 66 (7.58%)
occurrences (all)	6	4	8
Weight decreased			
subjects affected / exposed	8 / 35 (22.86%)	15 / 64 (23.44%)	14 / 66 (21.21%)
occurrences (all)	8	15	17
White blood cell count decreased			
subjects affected / exposed	0 / 35 (0.00%)	2 / 64 (3.13%)	6 / 66 (9.09%)
occurrences (all)	0	5	12
Nervous system disorders			
Cholinergic syndrome			
subjects affected / exposed	0 / 35 (0.00%)	0 / 64 (0.00%)	5 / 66 (7.58%)
occurrences (all)	0	0	6
Dizziness			
subjects affected / exposed	0 / 35 (0.00%)	3 / 64 (4.69%)	2 / 66 (3.03%)
occurrences (all)	0	5	3
Dysgeusia			
subjects affected / exposed	2 / 35 (5.71%)	12 / 64 (18.75%)	17 / 66 (25.76%)
occurrences (all)	2	12	20
Headache			

subjects affected / exposed	0 / 35 (0.00%)	3 / 64 (4.69%)	5 / 66 (7.58%)
occurrences (all)	0	3	6
Neuropathy peripheral			
subjects affected / exposed	0 / 35 (0.00%)	1 / 64 (1.56%)	4 / 66 (6.06%)
occurrences (all)	0	1	6
Paraesthesia			
subjects affected / exposed	0 / 35 (0.00%)	4 / 64 (6.25%)	10 / 66 (15.15%)
occurrences (all)	0	4	11
Peripheral motor neuropathy			
subjects affected / exposed	0 / 35 (0.00%)	1 / 64 (1.56%)	4 / 66 (6.06%)
occurrences (all)	0	1	6
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 35 (0.00%)	4 / 64 (6.25%)	5 / 66 (7.58%)
occurrences (all)	0	5	6
Polyneuropathy			
subjects affected / exposed	2 / 35 (5.71%)	19 / 64 (29.69%)	17 / 66 (25.76%)
occurrences (all)	2	26	18
Sleep disorder			
subjects affected / exposed	0 / 35 (0.00%)	4 / 64 (6.25%)	2 / 66 (3.03%)
occurrences (all)	0	4	4
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 35 (28.57%)	16 / 64 (25.00%)	10 / 66 (15.15%)
occurrences (all)	11	29	16
Leukopenia			
subjects affected / exposed	5 / 35 (14.29%)	27 / 64 (42.19%)	16 / 66 (24.24%)
occurrences (all)	6	53	29
Neutropenia			
subjects affected / exposed	6 / 35 (17.14%)	32 / 64 (50.00%)	25 / 66 (37.88%)
occurrences (all)	7	56	46
Thrombocytopenia			
subjects affected / exposed	5 / 35 (14.29%)	17 / 64 (26.56%)	16 / 66 (24.24%)
occurrences (all)	5	28	30
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	9 / 35 (25.71%)	31 / 64 (48.44%)	33 / 66 (50.00%)
occurrences (all)	14	50	58
Influenza like illness			
subjects affected / exposed	0 / 35 (0.00%)	4 / 64 (6.25%)	0 / 66 (0.00%)
occurrences (all)	0	5	0
Mucosal inflammation			
subjects affected / exposed	2 / 35 (5.71%)	13 / 64 (20.31%)	12 / 66 (18.18%)
occurrences (all)	3	16	18
Oedema			
subjects affected / exposed	1 / 35 (2.86%)	7 / 64 (10.94%)	6 / 66 (9.09%)
occurrences (all)	1	8	8
Oedema peripheral			
subjects affected / exposed	4 / 35 (11.43%)	16 / 64 (25.00%)	11 / 66 (16.67%)
occurrences (all)	4	18	13
Pain			
subjects affected / exposed	0 / 35 (0.00%)	2 / 64 (3.13%)	6 / 66 (9.09%)
occurrences (all)	0	2	6
Pyrexia			
subjects affected / exposed	5 / 35 (14.29%)	17 / 64 (26.56%)	13 / 66 (19.70%)
occurrences (all)	5	22	20
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 35 (5.71%)	9 / 64 (14.06%)	7 / 66 (10.61%)
occurrences (all)	4	9	9
Abdominal pain upper			
subjects affected / exposed	3 / 35 (8.57%)	4 / 64 (6.25%)	5 / 66 (7.58%)
occurrences (all)	3	4	7
Constipation			
subjects affected / exposed	5 / 35 (14.29%)	20 / 64 (31.25%)	16 / 66 (24.24%)
occurrences (all)	6	26	22
Diarrhoea			
subjects affected / exposed	12 / 35 (34.29%)	30 / 64 (46.88%)	27 / 66 (40.91%)
occurrences (all)	15	45	46
Dyspepsia			

subjects affected / exposed	0 / 35 (0.00%)	3 / 64 (4.69%)	5 / 66 (7.58%)
occurrences (all)	0	3	5
Nausea			
subjects affected / exposed	12 / 35 (34.29%)	34 / 64 (53.13%)	39 / 66 (59.09%)
occurrences (all)	13	51	71
Stomatitis			
subjects affected / exposed	2 / 35 (5.71%)	4 / 64 (6.25%)	7 / 66 (10.61%)
occurrences (all)	2	4	8
Vomiting			
subjects affected / exposed	6 / 35 (17.14%)	14 / 64 (21.88%)	21 / 66 (31.82%)
occurrences (all)	7	20	31
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 35 (0.00%)	1 / 64 (1.56%)	5 / 66 (7.58%)
occurrences (all)	0	1	5
Dyspnoea			
subjects affected / exposed	1 / 35 (2.86%)	5 / 64 (7.81%)	2 / 66 (3.03%)
occurrences (all)	1	5	3
Epistaxis			
subjects affected / exposed	1 / 35 (2.86%)	8 / 64 (12.50%)	7 / 66 (10.61%)
occurrences (all)	1	10	8
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	8 / 35 (22.86%)	29 / 64 (45.31%)	36 / 66 (54.55%)
occurrences (all)	8	32	40
Dry skin			
subjects affected / exposed	3 / 35 (8.57%)	4 / 64 (6.25%)	4 / 66 (6.06%)
occurrences (all)	3	4	5
Pruritus			
subjects affected / exposed	3 / 35 (8.57%)	0 / 64 (0.00%)	4 / 66 (6.06%)
occurrences (all)	3	0	4
Rash			
subjects affected / exposed	6 / 35 (17.14%)	10 / 64 (15.63%)	12 / 66 (18.18%)
occurrences (all)	7	11	19
Psychiatric disorders			

Anxiety			
subjects affected / exposed	2 / 35 (5.71%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences (all)	2	0	0
Insomnia			
subjects affected / exposed	0 / 35 (0.00%)	2 / 64 (3.13%)	3 / 66 (4.55%)
occurrences (all)	0	2	3
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 35 (0.00%)	1 / 64 (1.56%)	3 / 66 (4.55%)
occurrences (all)	0	1	5
Back pain			
subjects affected / exposed	0 / 35 (0.00%)	6 / 64 (9.38%)	4 / 66 (6.06%)
occurrences (all)	0	7	5
Bone pain			
subjects affected / exposed	0 / 35 (0.00%)	4 / 64 (6.25%)	1 / 66 (1.52%)
occurrences (all)	0	4	1
Myalgia			
subjects affected / exposed	0 / 35 (0.00%)	4 / 64 (6.25%)	0 / 66 (0.00%)
occurrences (all)	0	5	0
Pain in extremity			
subjects affected / exposed	0 / 35 (0.00%)	4 / 64 (6.25%)	2 / 66 (3.03%)
occurrences (all)	0	4	3
Infections and infestations			
Infection			
subjects affected / exposed	2 / 35 (5.71%)	7 / 64 (10.94%)	2 / 66 (3.03%)
occurrences (all)	2	8	2
Nasopharyngitis			
subjects affected / exposed	0 / 35 (0.00%)	1 / 64 (1.56%)	7 / 66 (10.61%)
occurrences (all)	0	2	9
Skin infection			
subjects affected / exposed	2 / 35 (5.71%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences (all)	2	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	10 / 35 (28.57%)	14 / 64 (21.88%)	19 / 66 (28.79%)
occurrences (all)	12	15	24

Hypokalaemia subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 6	3 / 64 (4.69%) 6	6 / 66 (9.09%) 6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 March 2015	New findings in the main effecting frequency of reported adverse events as well as adverse effects (e. g. Sepsis, interstitial pneumonitis, Stevens-Johnson Syndrome, HUS) were adapted to new findings respectively included in the protocol. Furthermore, some modifications in inclusion criteria, screening procedures mainly regarding CT examination (a three-phase contrast-enhanced spiral CT is recommended) and requirements for starting a new cycle of chemotherapy were made. Procedures during Follow-up were amended. More detailed information for management of dose omissions is given. In addition a new way for preparation and administration of nab-paclitaxel is described: due to a comparatively small volume of the nab-paclitaxel infusion, the infusion tube should be rinsed after application. NCCN-Guidelines Pancreatic Adenocarcinoma version 1.2015 is included.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The dropout rate during induction chemotherapy and the surgical conversion rate in the nab-paclitaxel plus gemcitabine group were higher than expected, which probably resulted in an underpowered study.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/33338442