



Clinical trial results:

Neoadjuvant plus adjuvant or only adjuvant nab-Paclitaxel plus Gemcitabine for resectable pancreatic cancer - The AIO-NEONAX trial (AIO-PAK-0313)

A prospective, randomized, controlled, phase II study of the AIO Pancreatic Cancer Group

Summary

EudraCT number	2013-005559-34
Trial protocol	DE AT
Global end of trial date	21 October 2022

Results information

Result version number	v1 (current)
This version publication date	10 August 2024
First version publication date	10 August 2024

Trial information

Trial identification

Sponsor protocol code	AIO-PAK-0313
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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	13 April 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 June 2021
Global end of trial reached?	Yes
Global end of trial date	21 October 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Disease free survival (DFS) rate assessed by imaging 18 months after randomization (improvement of DFS rate at 18 months in both arms to $\geq 55\%$)

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	03 July 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 127
Worldwide total number of subjects	127
EEA total number of subjects	127

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)	52
From 65 to 84 years	73
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The recruitment period of this clinical study was from 03 July 2015 (first patient randomised) to 23 October 2019 (last patient randomised). Patients were recruited at 22 study sites in Germany.

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	175 ^[1]
Intermediate milestone: Number of subjects	Randomized: 127
Number of subjects completed	118

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Violation of eligibility criteria during screening: 48
Reason: Number of subjects	Violation of eligibility criteria after randomization: 9

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Patients reported to have started the pre-assignment period comprise all patients who consented to study participation and participated in screening procedures. The number of patients reported as enrolled comprises all patients who were found eligible for study participation during screening.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A - perioperative

Arm description:

Neoadjuvant chemotherapy (2 cycles) preceding surgery (3 weeks after completion of chemotherapy) followed by adjuvant chemotherapy (4 cycles), starting within 12 weeks after surgery.

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

Dosage and administration details:

Nab-paclitaxel was administered in combination with gemcitabine on days 1, 8, and 15 of every 4-weeks treatment cycle. Nab-paclitaxel was to be administered via 30-minute i.v. infusions at a dose of 125 mg/m².

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

Dosage and administration details:

Gemcitabine was administered in combination with nab-paclitaxel on days 1, 8, and 15 of every 4-weeks treatment cycle. Gemcitabine was to be administered via 30-minute i.v. infusions at a dose of 1000 mg/m².

Arm title	Arm B - adjuvant
Arm description:	
Surgery followed by adjuvant chemotherapy (6 cycles) starting within 12 weeks after surgery	
Arm type	Experimental
Investigational medicinal product name	Nab-paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Nab-paclitaxel was administered in combination with gemcitabine on days 1, 8, and 15 of every 4-weeks treatment cycle. Nab-paclitaxel was to be administered via 30-minute i.v. infusions at a dose of 125 mg/m².

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

Dosage and administration details:

Gemcitabine was administered in combination with nab-paclitaxel on days 1, 8, and 15 of every 4-weeks treatment cycle. Gemcitabine was to be administered via 30-minute i.v. infusions at a dose of 1000 mg/m².

Number of subjects in period 1^[2]	Arm A - perioperative	Arm B - adjuvant
Started	59	59
All eligible patients /Full analysis set	59	59
Started neoadjuvant chemotherapy	54	0 ^[3]
Underwent resection	41	46
Started adjuvant chemotherapy	30	25
Completed	25	15
Not completed	34	44
Relapse	7	13
Disease progression	4	1
Patient's wish	7	2
Death	1	4
Intraop. irresectability	3	10
Lost to follow-up	-	3
Pat. choice/toxicity/clin. deterioration	6	9

Toxicity/clinical deterioration	4	-
R2-resected	2	2

Notes:

[2] - 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: The number of patients reported as enrolled comprises all patients who were found eligible for study participation during screening. Baseline data are reported for all patients who still met the eligibility criteria after randomization.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects for the milestone 'neoadjuvant treatment' is given as 0 because it was part of the study design not to give neoadjuvant treatment to patients in arm B.

Baseline characteristics

Reporting groups

Reporting group title	Arm A - perioperative
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Reporting group description:

Neoadjuvant chemotherapy (2 cycles) preceding surgery (3 weeks after completion of chemotherapy) followed by adjuvant chemotherapy (4 cycles), starting within 12 weeks after surgery.

Reporting group title	Arm B - adjuvant
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Reporting group description:

Surgery followed by adjuvant chemotherapy (6 cycles) starting within 12 weeks after surgery

Reporting group values	Arm A - perioperative	Arm B - adjuvant	Total
Number of subjects	59	59	118
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	65	68	
full range (min-max)	48 to 82	41 to 88	-
Gender categorical			
Units: Subjects			
Female	25	22	47
Male	34	37	71

End points

End points reporting groups

Reporting group title	Arm A - perioperative
Reporting group description: Neoadjuvant chemotherapy (2 cycles) preceding surgery (3 weeks after completion of chemotherapy) followed by adjuvant chemotherapy (4 cycles), starting within 12 weeks after surgery.	
Reporting group title	Arm B - adjuvant
Reporting group description: Surgery followed by adjuvant chemotherapy (6 cycles) starting within 12 weeks after surgery	

Primary: Rate of disease-free survival after 18 months

End point title	Rate of disease-free survival after 18 months
End point description:	
End point type	Primary
End point timeframe: DFS was defined as the time from randomisation to progression/relapse or death from any cause, whichever came first.	

End point values	Arm A - perioperative	Arm B - adjuvant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	59		
Units: Disease-free patients	15	9		

Statistical analyses

Statistical analysis title	Statistical analysis of primary endpoint
Comparison groups	Arm A - perioperative v Arm B - adjuvant
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	other ^[1]
P-value	= 0.25
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	1.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	4.75

Notes:

[1] - Analysis was explorative

Secondary: Median overall survival

End point title	Median overall survival
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End point description:

End point type	Secondary
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End point timeframe:

Overall survival was the time from randomisation to the date of death of any cause. For any patient for whom no date of death was known, the time to death was censored at the date of the patient's last recorded study visit.

End point values	Arm A - perioperative	Arm B - adjuvant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	59		
Units: months				
median (confidence interval 95%)	25.5 (19.7 to 29.7)	16.8 (12.5 to 22.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival milestone rates

End point title	Overall survival milestone rates
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End point description:

End point type	Secondary
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End point timeframe:

Overall survival was the time from randomisation to the date of death of any cause.

End point values	Arm A - perioperative	Arm B - adjuvant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	59		
Units: Surviving patients				
OS rate at 18 months	35	19		
OS rate at 36 months	11	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of disease-free survival after 36 months

End point title	Rate of disease-free survival after 36 months
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End point description:

End point type	Secondary
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End point timeframe:

See primary endpoint

End point values	Arm A - perioperative	Arm B - adjuvant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	59		
Units: Patients	5	5		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Median disease-free survival

End point title	Median disease-free survival
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End point description:

End point type	Post-hoc
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End point timeframe:

See primary endpoint

End point values	Arm A - perioperative	Arm B - adjuvant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	59		
Units: months				
median (confidence interval 95%)	11.4 (8.8 to 14.3)	5.1 (3.4 to 11.2)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are reported starting after first intake of study drug (arm A) or after pancreatic surgery (arm B), and until 28 days after the last dose of adjuvant systemic therapy or until the last study visit, whichever period was longer.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.1
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Reporting groups

Reporting group title	Arm A - perioperative
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Reporting group description:

Neoadjuvant chemotherapy (2 cycles) preceding surgery (3 weeks after completion of chemotherapy) followed by adjuvant chemotherapy (4 cycles), starting within 12 weeks after surgery.

Reporting group title	Arm B - adjuvant
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Reporting group description:

Surgery followed by adjuvant chemotherapy (6 cycles) starting within 12 weeks after surgery

Serious adverse events	Arm A - perioperative	Arm B - adjuvant	
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 57 (56.14%)	19 / 57 (33.33%)	
number of deaths (all causes)	1	4	
number of deaths resulting from adverse events	0	4	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic carcinoma recurrent			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arterial haemorrhage			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypertensive crisis			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Thrombophlebitis			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 57 (1.75%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyrexia			
subjects affected / exposed	4 / 57 (7.02%)	3 / 57 (5.26%)	
occurrences causally related to treatment / all	4 / 4	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Aspiration			

subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 57 (3.51%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 57 (0.00%)	2 / 57 (3.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device occlusion			
subjects affected / exposed	4 / 57 (7.02%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Klebsiella test positive			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anastomotic ulcer			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pancreatic leak			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 57 (1.75%)	2 / 57 (3.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic encephalopathy			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Syncope			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	2 / 57 (3.51%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic microangiopathy			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	3 / 57 (5.26%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Colitis			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 57 (3.51%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea haemorrhagic			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 57 (1.75%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal pain			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic fistula			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			

subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	1 / 57 (1.75%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stenosis			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary fistula			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	3 / 57 (5.26%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal vein thrombosis			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Myositis			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	2 / 57 (3.51%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis infective			

subjects affected / exposed	2 / 57 (3.51%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	4 / 57 (7.02%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	2 / 7	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	0 / 57 (0.00%)	2 / 57 (3.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 57 (3.51%)	2 / 57 (3.51%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 57 (1.75%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Staphylococcal infection			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			

subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal infection			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Abnormal loss of weight			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	2 / 57 (3.51%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A - perioperative	Arm B - adjuvant	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 57 (96.49%)	30 / 57 (52.63%)	
Investigations			
C-reactive protein increased			
subjects affected / exposed	6 / 57 (10.53%)	2 / 57 (3.51%)	
occurrences (all)	10	2	

Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 57 (5.26%)	0 / 57 (0.00%)	
occurrences (all)	3	0	
Neutrophil count decreased			
subjects affected / exposed	4 / 57 (7.02%)	1 / 57 (1.75%)	
occurrences (all)	6	1	
Platelet count decreased			
subjects affected / exposed	4 / 57 (7.02%)	0 / 57 (0.00%)	
occurrences (all)	6	0	
Weight decreased			
subjects affected / exposed	15 / 57 (26.32%)	7 / 57 (12.28%)	
occurrences (all)	17	7	
Weight increased			
subjects affected / exposed	3 / 57 (5.26%)	0 / 57 (0.00%)	
occurrences (all)	3	0	
White blood cell count decreased			
subjects affected / exposed	15 / 57 (26.32%)	7 / 57 (12.28%)	
occurrences (all)	17	7	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	5 / 57 (8.77%)	6 / 57 (10.53%)	
occurrences (all)	5	6	
Headache			
subjects affected / exposed	4 / 57 (7.02%)	1 / 57 (1.75%)	
occurrences (all)	6	1	
Peripheral sensory neuropathy			
subjects affected / exposed	4 / 57 (7.02%)	0 / 57 (0.00%)	
occurrences (all)	5	0	
Polyneuropathy			
subjects affected / exposed	19 / 57 (33.33%)	9 / 57 (15.79%)	
occurrences (all)	28	11	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	14 / 57 (24.56%)	5 / 57 (8.77%)	
occurrences (all)	18	10	
Granulocytopenia			

subjects affected / exposed	4 / 57 (7.02%)	0 / 57 (0.00%)	
occurrences (all)	7	0	
Leukopenia			
subjects affected / exposed	17 / 57 (29.82%)	6 / 57 (10.53%)	
occurrences (all)	25	6	
Neutropenia			
subjects affected / exposed	16 / 57 (28.07%)	9 / 57 (15.79%)	
occurrences (all)	35	14	
Thrombocytopenia			
subjects affected / exposed	13 / 57 (22.81%)	3 / 57 (5.26%)	
occurrences (all)	16	5	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	28 / 57 (49.12%)	15 / 57 (26.32%)	
occurrences (all)	39	21	
General physical health deterioration			
subjects affected / exposed	3 / 57 (5.26%)	1 / 57 (1.75%)	
occurrences (all)	3	1	
Mucosal inflammation			
subjects affected / exposed	4 / 57 (7.02%)	4 / 57 (7.02%)	
occurrences (all)	5	4	
Oedema peripheral			
subjects affected / exposed	11 / 57 (19.30%)	7 / 57 (12.28%)	
occurrences (all)	15	11	
Pain			
subjects affected / exposed	3 / 57 (5.26%)	0 / 57 (0.00%)	
occurrences (all)	3	0	
Pyrexia			
subjects affected / exposed	8 / 57 (14.04%)	8 / 57 (14.04%)	
occurrences (all)	11	8	
Influenza like illness			
subjects affected / exposed	2 / 57 (3.51%)	3 / 57 (5.26%)	
occurrences (all)	3	3	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	7 / 57 (12.28%)	4 / 57 (7.02%)	
occurrences (all)	7	1	
Abdominal pain upper			
subjects affected / exposed	5 / 57 (8.77%)	1 / 57 (1.75%)	
occurrences (all)	5	1	
Constipation			
subjects affected / exposed	18 / 57 (31.58%)	5 / 57 (8.77%)	
occurrences (all)	20	5	
Diarrhoea			
subjects affected / exposed	14 / 57 (24.56%)	10 / 57 (17.54%)	
occurrences (all)	16	13	
Flatulence			
subjects affected / exposed	3 / 57 (5.26%)	3 / 57 (5.26%)	
occurrences (all)	3	3	
Nausea			
subjects affected / exposed	23 / 57 (40.35%)	11 / 57 (19.30%)	
occurrences (all)	29	12	
Stomatitis			
subjects affected / exposed	5 / 57 (8.77%)	0 / 57 (0.00%)	
occurrences (all)	6	0	
Vomiting			
subjects affected / exposed	9 / 57 (15.79%)	6 / 57 (10.53%)	
occurrences (all)	12	11	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 57 (5.26%)	3 / 57 (5.26%)	
occurrences (all)	3	5	
Dyspnoea			
subjects affected / exposed	4 / 57 (7.02%)	3 / 57 (5.26%)	
occurrences (all)	4	4	
Epistaxis			
subjects affected / exposed	8 / 57 (14.04%)	4 / 57 (7.02%)	
occurrences (all)	10	4	
Skin and subcutaneous tissue disorders			

Alopecia subjects affected / exposed occurrences (all)	28 / 57 (49.12%) 30	9 / 57 (15.79%) 10	
Rash subjects affected / exposed occurrences (all)	13 / 57 (22.81%) 14	2 / 57 (3.51%) 3	
Pruritus subjects affected / exposed occurrences (all)	3 / 57 (5.26%) 3	2 / 57 (3.51%) 2	
Psychiatric disorders Sleep disorder subjects affected / exposed occurrences (all)	5 / 57 (8.77%) 5	1 / 57 (1.75%) 1	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	3 / 57 (5.26%) 3	4 / 57 (7.02%) 4	
Back pain subjects affected / exposed occurrences (all)	3 / 57 (5.26%) 3	0 / 57 (0.00%) 0	
Infections and infestations Pneumonia subjects affected / exposed occurrences (all)	3 / 57 (5.26%) 3	0 / 57 (0.00%) 0	
Urinary tract infection subjects affected / exposed occurrences (all)	4 / 57 (7.02%) 5	3 / 57 (5.26%) 4	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	9 / 57 (15.79%) 13	9 / 57 (15.79%) 12	
Hypokalaemia subjects affected / exposed occurrences (all)	5 / 57 (8.77%) 5	2 / 57 (3.51%) 2	
Type 2 diabetes mellitus			

subjects affected / exposed	3 / 57 (5.26%)	1 / 57 (1.75%)	
occurrences (all)	3	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 September 2016	- Inclusion criteria serum total bilirubin level, ALT, and AST $\leq 2.5 \times$ ULN were determined as not necessary for enrolment or randomization, but before the start of the neoadjuvant chemotherapy - Biliary decompression in case of biliary obstruction required only for patients randomized receiving neoadjuvant chemotherapy (arm A); post-interventional bilirubin level criterion deleted. - Addition of cytologically confirmed analyses of the PDAC - Change of study biometrician, extension of timelines, number of planned participating centres increased, update of RSI (IB 18.0) - The choice of the needle for the biopsies was left to the investigator's discretion - Inclusion of patients older than 75 years of age allowed - Accidental or intentional overdoses to be reported as (serious) adverse events - Determination of (suspected) pregnancies in a partner of childbearing potential of a male subject as reportable events - Clarification of the blood samples taken for Translational Research
25 June 2018	- Time of recruitment of eligible patients extended from 36 to 54 months - Extension of timelines - Patient to be taken off the treatment protocol if toxicity required a cycle delay of more than 21 days instead of 4 weeks - New rules for dose omissions introduced - The current versions of the Investigator's brochure of nab-paclitaxel and the SmPC of gemcitabine defined as reference documents - Addition of inclusion criterion "measurable tumour according to RECIST 1.1". - Addition of discontinuation "criterion disease progression also according to RECIST 1.1", borderline cases to be discussed with CI (7.9) - Introduction of requirements for registration and authorization of the trial, ethics committees, investigator qualifications, and labelling, in case sites outside Germany were added - Definition of reporting deadlines for SAEs with context
14 June 2019	- Reduction of timelines - To clarify the wording for the observation time after randomization, observation period of patients set to 36 months after randomization - To assess tumour response and recurrence, imaging data (CT scans, MRI scans) were additionally obtained during the trial and analysed centrally for the following time points: Baseline, Before the surgery, After the surgery, End of trial, 18 months after randomization, In case of relapse - The reduced number of cases was associated with a reduction in the power of the study. Necessary adjustments included: ▪ Number of patients to be assessed for eligibility reduced from 190 to 172 ▪ Number of patients to be allocated to trial reduced from 166 to 126 ▪ Number of patients to be analysed reduced from 116 to 88 (44 per arm) - Allowed treatment delay between two treatment cycles reduced from 4 weeks to <21 days - Clarification of definition of observation time as 3-years after randomization for OS, DFS and possible second / further line treatment, documentation of staging procedures - Update of the Rationale according to new literature - Changes regarding the reference safety information

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/30594153>

<http://www.ncbi.nlm.nih.gov/pubmed/36209981>