



Clinical trial results:

A MULTINATIONAL, RANDOMIZED, PHASE II STUDY OF THE COMBINATION OF NAB-PACLITAXEL AND GEMCITABINE WITH OR WITHOUT IL-6R INHIBITOR, TOCILIZUMAB, AS FIRST-LINE TREATMENT IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC PANCREATIC CANCER.

Summary

EudraCT number	2016-000643-13
Trial protocol	DK NO
Global end of trial date	18 July 2022

Results information

Result version number	v1 (current)
This version publication date	22 July 2023
First version publication date	22 July 2023

Trial information

Trial identification

Sponsor protocol code	GI1612
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02767557
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Herlev & Gentofte Hospital, Department of Oncology
Sponsor organisation address	Borgmester Ib Juuls Vej 1, Herlev, Denmark, 2730
Public contact	Inna Chen, Herlev & Gentofte Hospital, +45 38682898, inna.chen@regionh.dk
Scientific contact	Inna Chen, Herlev & Gentofte Hospital, +45 38682898, inna.chen@regionh.dk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 January 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 July 2022
Global end of trial reached?	Yes
Global end of trial date	18 July 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare overall survival at 6 months of gemcitabine/nab-paclitaxel plus tocilizumab and gemcitabine/nab-paclitaxel.

Protection of trial subjects:

Patients that signed informed consent and fulfilling eligibility criteria were included. Continued monitoring of standard safety parameters during treatment.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 January 2017
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	Norway: 1
Country: Number of subjects enrolled	Denmark: 146
Worldwide total number of subjects	147
EEA total number of subjects	147

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)	62
From 65 to 84 years	85
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was opened for recruitment in January 2017 and closed for enrollment in July 2021 . Patients were included at 2 sites, Copenhagen University Hospital - Herlev and Gentofte in Denmark and Oslo University Hospital, Norway.

Pre-assignment

Screening details:

Eligible patients were ≥ 18 years with locally advanced or metastatic pancreatic cancer, who had not previously received treatment in the advanced setting, ECOG PS 0-1, mGPS ≥ 1 , with measureable disease and adequate organ and hematologic function.

Period 1

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

Blinding implementation details:

Prior to randomised portion of the trial, a safety cohort of 6 participants recieved experimental treatment (unrandomised). 141 participants were randomly assigned to experimental and standard treatment, stratification by ECOG PS (0 vs 1) and stage of disease (locally advanced vs metastatic.

Arms

Are arms mutually exclusive?	Yes
Arm title	Safety Cohort

Arm description:

Gemcitabine and nab-paclitaxel in combination with tocilizumab.

Treatment continued until disease progression, unacceptable toxicity, pregnancy, patient's withdrawal of the informed consent at his/hers own request or investigator's discretion

Arm type	Experimental
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intracavernous use

Dosage and administration details:

1000 mg/m² i.v. on day 1, day 8 and day 15 of every 28 day cycle.

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:

125 mg/m² i.v. on day 1, day 8 and day 15 of every 28 day cycle.

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

Dosage and administration details:

8 mg/kg given i.v. on day 1 of every 28 day cycle.

Arm title	Gem/Nab/Toc
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Arm description:

Gemcitabine and nab-paclitaxel in combination with tocilizumab.

Treatment continued until disease progression, unacceptable toxicity, pregnancy, patient's withdrawal of the informed consent at his/hers own request or investigator's discretion

Arm type	Experimental
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intracavernous use

Dosage and administration details:

1000 mg/m² i.v. on day 1, day 8 and day 15 of every 28 day cycle.

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:

125 mg/m² i.v. on day 1, day 8 and day 15 of every 28 day cycle.

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

Dosage and administration details:

8 mg/kg given i.v. on day 1 of every 28 day cycle.

Arm title	Gem/Nab
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Arm description:

Gemcitabine and nab-paclitaxel

Treatment continued until disease progression, unacceptable toxicity, pregnancy, patient's withdrawal of the informed consent at his/hers own request or investigator's discretion

Arm type	Active comparator
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intracavernous use

Dosage and administration details:

1000 mg/m² i.v. on day 1, day 8 and day 15 of every 28 day cycle.

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:

125 mg/m² i.v. on day 1, day 8 and day 15 of every 28 day cycle.

Number of subjects in period 1	Safety Cohort	Gem/Nab/Toc	Gem/Nab
Started	6	70	71
Completed	5	47	53
Not completed	1	23	18
Adverse event, serious fatal	-	4	2
Consent withdrawn by subject	-	2	5
Physician decision	-	2	1
Adverse event, non-fatal	-	9	6
Death from disease under study	1	4	3
Resection of tumor	-	2	1

Baseline characteristics

Reporting groups

Reporting group title	Safety Cohort
Reporting group description: Gemcitabine and nab-paclitaxel in combination with tocilizumab. Treatment continued until disease progression, unacceptable toxicity, pregnancy, patient's withdrawal of the informed consent at his/hers own request or investigator's discretion	
Reporting group title	Gem/Nab/Toc
Reporting group description: Gemcitabine and nab-paclitaxel in combination with tocilizumab. Treatment continued until disease progression, unacceptable toxicity, pregnancy, patient's withdrawal of the informed consent at his/hers own request or investigator's discretion	
Reporting group title	Gem/Nab
Reporting group description: Gemcitabine and nab-paclitaxel Treatment continued until disease progression, unacceptable toxicity, pregnancy, patient's withdrawal of the informed consent at his/hers own request or investigator's discretion	

Reporting group values	Safety Cohort	Gem/Nab/Toc	Gem/Nab
Number of subjects	6	70	71
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 full range (min-max)	69.5 49 to 76	68 34 to 84	67 36 to 84
Gender categorical Units: Subjects			
Female	3	30	28
Male	3	40	43
ECOG Performance status Units: Subjects			
ECOG PS 0	2	26	27
ECOG PS 1	4	44	44
Disease Stage Units: Subjects			
Locally advanced	0	5	6
Metastatic	6	65	65

Reporting group values	Total		
Number of subjects	147		
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			
full range (min-max)	-		
Gender categorical			
Units: Subjects			
Female	61		
Male	86		
ECOG Performance status			
Units: Subjects			
ECOG PS 0	55		
ECOG PS 1	92		
Disease Stage			
Units: Subjects			
Locally advanced	11		
Metastatic	136		

Subject analysis sets

Subject analysis set title	Efficacy analysis
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Patients randomised to either Gem/Nab/Toc or Gem/Nab and recieved at treatment at least once	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
Both the patients that were included in the safety cohort (Gem/Nab/Toc) and those randomised to either Gem/Nab/Toc or Gem/Nab and having received treatment at least once.	

Reporting group values	Efficacy analysis	Safety	
Number of subjects	141	147	
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 full range (min-max)	67 34 to 84	67 34 to 84	
Gender categorical Units: Subjects			
Female Male	58 83	61 86	
ECOG Performance status Units: Subjects			
ECOG PS 0 ECOG PS 1	53 88	55 92	
Disease Stage Units: Subjects			
Locally advanced Metastatic	11 130	11 136	

End points

End points reporting groups

Reporting group title	Safety Cohort
Reporting group description: Gemcitabine and nab-paclitaxel in combination with tocilizumab. Treatment continued until disease progression, unacceptable toxicity, pregnancy, patient's withdrawal of the informed consent at his/hers own request or investigator's discretion	
Reporting group title	Gem/Nab/Toc
Reporting group description: Gemcitabine and nab-paclitaxel in combination with tocilizumab. Treatment continued until disease progression, unacceptable toxicity, pregnancy, patient's withdrawal of the informed consent at his/hers own request or investigator's discretion	
Reporting group title	Gem/Nab
Reporting group description: Gemcitabine and nab-paclitaxel Treatment continued until disease progression, unacceptable toxicity, pregnancy, patient's withdrawal of the informed consent at his/hers own request or investigator's discretion	
Subject analysis set title	Efficacy analysis
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Patients randomised to either Gem/Nab/Toc or Gem/Nab and recieved at treatment at least once	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description: Both the patients that were included in the safety cohort (Gem/Nab/Toc) and those randomised to either Gem/Nab/Toc or Gem/Nab and having received treatment at least once.	

Primary: OS rate at 6 months

End point title	OS rate at 6 months ^[1]
End point description:	
End point type	Primary
End point timeframe: 6 months from randomisation	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Safety cohort of 6 patients is not included in the efficacy endpoint, which was analysed in for patients in the randomised part of the trial

End point values	Gem/Nab/Toc	Gem/Nab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	71		
Units: percent				
number (confidence interval 95%)	68.6 (56.3 to 78.1)	62 (49.6 to 72.1)		

Statistical analyses

Statistical analysis title	Comparison of OS rate at specific timepoint
Comparison groups	Gem/Nab/Toc v Gem/Nab
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.409
Method	z-test

Secondary: Overall Survival

End point title	Overall Survival ^[2]
End point description:	

End point type	Secondary
End point timeframe:	
Time from randomisation to death	

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Safety cohort of 6 patients is not included in the efficacy endpoint, which was analysed in for patients in the randomised part of the trial

End point values	Gem/Nab/Toc	Gem/Nab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	71		
Units: months				
median (confidence interval 95%)	8.4 (6.7 to 11.4)	8.0 (5.9 to 9.8)		

Statistical analyses

Statistical analysis title	Overall survival
Comparison groups	Gem/Nab/Toc v Gem/Nab
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.096
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.05

Secondary: Progression free survival

End point title	Progression free survival ^[3]
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End point description:

End point type	Secondary
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End point timeframe:

time from randomisation to radiological progression or death

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Safety cohort of 6 patients is not included in the efficacy endpoint, which was analysed in for patients in the randomised part of the trial

End point values	Gem/Nab/Toc	Gem/Nab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	71		
Units: month				
median (confidence interval 95%)	5.6 (3.9 to 7.4)	5.5 (3.5 to 7.0)		

Statistical analyses

Statistical analysis title	PFS
Comparison groups	Gem/Nab/Toc v Gem/Nab
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.339
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.19

Secondary: Objective response rate

End point title	Objective response rate ^[4]
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End point description:

End point type	Secondary
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End point timeframe:

tumor assessment every 8 weeks from treatment start

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Safety cohort of 6 patients is not included in the efficacy endpoint, which was analysed in for patients in the randomised part of the trial

End point values	Gem/Nab/Toc	Gem/Nab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	71		
Units: percent				
number (confidence interval 95%)	37.1 (25.9 to 45.9)	35.2 (24.2 to 47.5)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Time from treatment start to 30 days after last treatment

Adverse event reporting additional description:

For non-serious AE section, only AEs with causal relationship to treatment (AR) are listed (numbers includes subjects/occurrences reported as SARs as well).

Assessment type	Systematic
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Dictionary used

Dictionary name	CTCAE
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Dictionary version	4
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Reporting groups

Reporting group title	Safety Cohort
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Reporting group description:

Gemcitabine and nab-paclitaxel in combination with tocilizumab.

Treatment continued until disease progression, unacceptable toxicity, pregnancy, patient's withdrawal of the informed consent at his/hers own request or investigator's discretion

Reporting group title	Gem/Nab/Toc
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Reporting group description:

Gemcitabine and nab-paclitaxel in combination with tocilizumab.

Treatment continued until disease progression, unacceptable toxicity, pregnancy, patient's withdrawal of the informed consent at his/hers own request or investigator's discretion

Reporting group title	Gem/Nab
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Reporting group description:

Gemcitabine and nab-paclitaxel

Treatment continued until disease progression, unacceptable toxicity, pregnancy, patient's withdrawal of the informed consent at his/hers own request or investigator's discretion

Serious adverse events	Safety Cohort	Gem/Nab/Toc	Gem/Nab
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 6 (50.00%)	49 / 70 (70.00%)	40 / 71 (56.34%)
number of deaths (all causes)	6	70	71
number of deaths resulting from adverse events	0	4	2
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 6 (0.00%)	2 / 70 (2.86%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 6 (0.00%)	1 / 70 (1.43%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombotic angiopathy			

subjects affected / exposed	0 / 6 (0.00%)	1 / 70 (1.43%)	0 / 71 (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
Portal vein thrombosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 70 (1.43%)	0 / 71 (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
Capillary leak syndrome			
subjects affected / exposed	0 / 6 (0.00%)	1 / 70 (1.43%)	0 / 71 (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
Pulmonary embolism			
subjects affected / exposed	1 / 6 (16.67%)	0 / 70 (0.00%)	3 / 71 (4.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
General disorders and administration site conditions			
Edema limbs			
subjects affected / exposed	0 / 6 (0.00%)	2 / 70 (2.86%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fever			
subjects affected / exposed	0 / 6 (0.00%)	2 / 70 (2.86%)	2 / 71 (2.82%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
flu like symptoms			
subjects affected / exposed	0 / 6 (0.00%)	0 / 70 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)	1 / 70 (1.43%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonitis			
subjects affected / exposed	1 / 6 (16.67%)	4 / 70 (5.71%)	5 / 71 (7.04%)
occurrences causally related to treatment / all	1 / 1	4 / 4	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 6 (0.00%)	1 / 70 (1.43%)	0 / 71 (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
Pneumothorax			
subjects affected / exposed	0 / 6 (0.00%)	1 / 70 (1.43%)	0 / 71 (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
Hypoxia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 70 (0.00%)	0 / 71 (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
Psychiatric disorders			
Mania			
subjects affected / exposed	0 / 6 (0.00%)	0 / 70 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	0 / 6 (0.00%)	0 / 70 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Neutropenia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 70 (2.86%)	0 / 71 (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
Thrombocytopenia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 70 (1.43%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hyperbilirubinaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 70 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 6 (0.00%)	2 / 70 (2.86%)	0 / 71 (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
Cardiac failure			
subjects affected / exposed	0 / 6 (0.00%)	1 / 70 (1.43%)	0 / 71 (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
Supraventricular tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 70 (1.43%)	0 / 71 (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
Tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 70 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Hepatic encephalopathy			
subjects affected / exposed	0 / 6 (0.00%)	1 / 70 (1.43%)	0 / 71 (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
Cerebral infarction			
subjects affected / exposed	0 / 6 (0.00%)	2 / 70 (2.86%)	3 / 71 (4.23%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anemia			

subjects affected / exposed	0 / 6 (0.00%)	2 / 70 (2.86%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 6 (0.00%)	4 / 70 (5.71%)	3 / 71 (4.23%)
occurrences causally related to treatment / all	0 / 0	4 / 4	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Duodenal ulcer			
subjects affected / exposed	0 / 6 (0.00%)	1 / 70 (1.43%)	0 / 71 (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
Constipation			
subjects affected / exposed	0 / 6 (0.00%)	7 / 70 (10.00%)	3 / 71 (4.23%)
occurrences causally related to treatment / all	0 / 0	0 / 9	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 6 (16.67%)	7 / 70 (10.00%)	2 / 71 (2.82%)
occurrences causally related to treatment / all	1 / 1	8 / 8	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 6 (0.00%)	1 / 70 (1.43%)	0 / 71 (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
Pancreatitis			
subjects affected / exposed	0 / 6 (0.00%)	2 / 70 (2.86%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 70 (1.43%)	0 / 71 (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
Vomiting			

subjects affected / exposed	0 / 6 (0.00%)	3 / 70 (4.29%)	3 / 71 (4.23%)
occurrences causally related to treatment / all	0 / 0	3 / 3	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	2 / 70 (2.86%)	3 / 71 (4.23%)
occurrences causally related to treatment / all	0 / 0	1 / 2	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis intestinal perforated			
subjects affected / exposed	0 / 6 (0.00%)	2 / 70 (2.86%)	0 / 71 (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
Nausea			
subjects affected / exposed	0 / 6 (0.00%)	1 / 70 (1.43%)	3 / 71 (4.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 70 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Gallbladder obstruction			
subjects affected / exposed	0 / 6 (0.00%)	1 / 70 (1.43%)	0 / 71 (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
Hepatic failure			
subjects affected / exposed	0 / 6 (0.00%)	1 / 70 (1.43%)	0 / 71 (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
Haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	1 / 70 (1.43%)	0 / 71 (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
Renal and urinary disorders			

Bladder spasm			
subjects affected / exposed	0 / 6 (0.00%)	1 / 70 (1.43%)	0 / 71 (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
Urinary retention			
subjects affected / exposed	0 / 6 (0.00%)	1 / 70 (1.43%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 70 (1.43%)	0 / 71 (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
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 70 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 6 (16.67%)	9 / 70 (12.86%)	7 / 71 (9.86%)
occurrences causally related to treatment / all	1 / 1	10 / 12	5 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 6 (0.00%)	15 / 70 (21.43%)	7 / 71 (9.86%)
occurrences causally related to treatment / all	0 / 0	14 / 19	5 / 8
deaths causally related to treatment / all	0 / 0	2 / 2	1 / 1
Infection unknown focus			
subjects affected / exposed	0 / 6 (0.00%)	3 / 70 (4.29%)	5 / 71 (7.04%)
occurrences causally related to treatment / all	0 / 0	3 / 3	7 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 70 (1.43%)	0 / 71 (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

Abscess			
subjects affected / exposed	0 / 6 (0.00%)	5 / 70 (7.14%)	2 / 71 (2.82%)
occurrences causally related to treatment / all	0 / 0	2 / 6	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 6 (0.00%)	1 / 70 (1.43%)	0 / 71 (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
Urinary tract infection			
subjects affected / exposed	1 / 6 (16.67%)	2 / 70 (2.86%)	2 / 71 (2.82%)
occurrences causally related to treatment / all	1 / 1	1 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary tract infection			
subjects affected / exposed	1 / 6 (16.67%)	2 / 70 (2.86%)	2 / 71 (2.82%)
occurrences causally related to treatment / all	1 / 1	0 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
infection due to necrosis/liver infarct			
subjects affected / exposed	0 / 6 (0.00%)	1 / 70 (1.43%)	0 / 71 (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
Abdominal infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 70 (1.43%)	0 / 71 (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
Epididymitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 70 (1.43%)	0 / 71 (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
Peritonitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 70 (1.43%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			

subjects affected / exposed	0 / 6 (0.00%)	0 / 70 (0.00%)	4 / 71 (5.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 70 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary candida infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 70 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 70 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Ketosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 70 (1.43%)	0 / 71 (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
Dehydration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 70 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acidosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 70 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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	Safety Cohort	Gem/Nab/Toc	Gem/Nab
Total subjects affected by non-serious adverse events subjects affected / exposed	6 / 6 (100.00%)	70 / 70 (100.00%)	71 / 71 (100.00%)
Investigations			
Thrombocytopenia subjects affected / exposed	3 / 6 (50.00%)	54 / 70 (77.14%)	35 / 71 (49.30%)
occurrences (all)	10	292	124
Neutropenia subjects affected / exposed	4 / 6 (66.67%)	51 / 70 (72.86%)	29 / 71 (40.85%)
occurrences (all)	10	212	75
Alanine aminotransferase increased subjects affected / exposed	2 / 6 (33.33%)	37 / 70 (52.86%)	17 / 71 (23.94%)
occurrences (all)	6	71	30
Nervous system disorders			
Peripheral sensory neuropathy subjects affected / exposed	5 / 6 (83.33%)	46 / 70 (65.71%)	46 / 71 (64.79%)
occurrences (all)	13	113	100
Peripheral motor neuropathy subjects affected / exposed	3 / 6 (50.00%)	22 / 70 (31.43%)	16 / 71 (22.54%)
occurrences (all)	7	46	33
Dizziness subjects affected / exposed	1 / 6 (16.67%)	2 / 70 (2.86%)	4 / 71 (5.63%)
occurrences (all)	2	2	9
General disorders and administration site conditions			
Fatigue subjects affected / exposed	3 / 6 (50.00%)	48 / 70 (68.57%)	45 / 71 (63.38%)
occurrences (all)	7	150	104
Fever subjects affected / exposed	2 / 6 (33.33%)	4 / 70 (5.71%)	10 / 71 (14.08%)
occurrences (all)	2	6	19
flu/flu like symptoms subjects affected / exposed	1 / 6 (16.67%)	5 / 70 (7.14%)	6 / 71 (8.45%)
occurrences (all)	1	5	6
Oedema subjects affected / exposed	2 / 6 (33.33%)	29 / 70 (41.43%)	17 / 71 (23.94%)
occurrences (all)	5	68	35
Pain	Additional description: Includes different verbatims such as pain + abdominal		

	pain+ pain in extremity+ chest wall pain		
subjects affected / exposed	1 / 6 (16.67%)	11 / 70 (15.71%)	5 / 71 (7.04%)
occurrences (all)	2	16	5
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 6 (16.67%)	7 / 70 (10.00%)	12 / 71 (16.90%)
occurrences (all)	2	9	27
Febrile neutropenia			
subjects affected / exposed	1 / 6 (16.67%)	6 / 70 (8.57%)	3 / 71 (4.23%)
occurrences (all)	1	6	3
Immune system disorders			
Allergic reaction			
subjects affected / exposed	2 / 6 (33.33%)	2 / 70 (2.86%)	3 / 71 (4.23%)
occurrences (all)	3	5	3
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 6 (66.67%)	44 / 70 (62.86%)	45 / 71 (63.38%)
occurrences (all)	14	102	91
Nausea			
subjects affected / exposed	3 / 6 (50.00%)	41 / 70 (58.57%)	41 / 71 (57.75%)
occurrences (all)	4	90	79
Vomiting			
subjects affected / exposed	2 / 6 (33.33%)	22 / 70 (31.43%)	21 / 71 (29.58%)
occurrences (all)	2	35	30
Haemorrhage	Additional description: Includes different types of hemorrhage; mostly as GI but also vaginal , hematuria, epistaxis, subconjunctiva		
subjects affected / exposed	2 / 6 (33.33%)	8 / 70 (11.43%)	6 / 71 (8.45%)
occurrences (all)	3	11	7
Mucositis			
subjects affected / exposed	4 / 6 (66.67%)	20 / 70 (28.57%)	14 / 71 (19.72%)
occurrences (all)	10	34	22
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	1 / 6 (16.67%)	7 / 70 (10.00%)	7 / 71 (9.86%)
occurrences (all)	1	8	12
Dyspnoea			

subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	3 / 70 (4.29%) 4	5 / 71 (7.04%) 7
Skin and subcutaneous tissue disorders			
Nail ridging			
subjects affected / exposed	2 / 6 (33.33%)	4 / 70 (5.71%)	4 / 71 (5.63%)
occurrences (all)	4	6	9
Rash			
subjects affected / exposed	1 / 6 (16.67%)	12 / 70 (17.14%)	12 / 71 (16.90%)
occurrences (all)	1	22	15
Infections and infestations			
Sepsis			
subjects affected / exposed	0 / 6 (0.00%)	11 / 70 (15.71%)	5 / 71 (7.04%)
occurrences (all)	0	14	5
Infection	Additional description: includes infections of unknown focus, Pneumonia, Urinary tract, Clostridium difficile, Upper Respiratory tract, Pulmonary candida, Biliary tract , Cholecystitis, groin, Epididymitis, Herpes, Eye, Nail , Erysipelas, Skin, Wound ,foot		
subjects affected / exposed	2 / 6 (33.33%)	28 / 70 (40.00%)	28 / 71 (39.44%)
occurrences (all)	7	55	43
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	3 / 6 (50.00%)	31 / 70 (44.29%)	32 / 71 (45.07%)
occurrences (all)	5	53	60
Hypokalaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 70 (0.00%)	4 / 71 (5.63%)
occurrences (all)	0	0	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 October 2016	Additional laboratory test for lipid profile at start of each cycle. Additional tumor biopsy at time of progression (if feasible and at the discretion of investigator)
01 May 2018	- Additional center at Oslo University Hospital - additional exploratory objective and endpoints were added to assess whether inhibition of IL-6R has an impact on cachexia in patients with locally advanced or metastatic pancreatic cancer - Adjustment to study timelines
04 December 2018	After interim safety analysis - implementation of Mandatory supportive treatment with G-CSF: In cycle 1 all patients will receive G-CSF (self-administered) on day 9, i.e. 24 hours after administration of chemotherapy on day 8, or on day 8 in the clinic if self-administration is not an option. Upon reference all PACTO patients must be admitted and if ANC < 1.0 x 10 ⁹ /L is observed, G-CSF and antibiotics (tazocin and metronidazole) will be initiated, regardless of fever or CRP. Antibiotics should be adjusted / discontinued dependent on clinic thereafter. Additionally clarification and corrections in the protocol based on comments from Norwegian Competent authority
08 December 2019	Adjustment of study timelines

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported