Clinical trial results:
A Multi-Institutional, Single Arm, Two-Stage Phase II Trial of Nab-Paclitaxel and Gemcitabine for First-Line Treatment of Patients with Advanced or Metastatic Cholangiocarcinoma

Summary

EudraCT number	2015-002066-24
Trial protocol	AT
Global end of trial date	01 October 2017

Results information

Result version number	v1 (current)
This version publication date	08 March 2025
First version publication date	08 March 2025
Summary attachment (see zip file)	2015-002066-24 results posted 20Feb2025 (2015-002066-24 results posted 20Feb2025.pdf)

Trial information

Trial identification

Sponsor protocol code	PrE0204

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02181634
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medizinische Universität Wien
Sponsor organisation address	Spitalgasse 23, Vienna, Austria, 1090
Public contact	Prof. Werner Scheithauer, Medizinische Universität Wien, werner.scheithauer@meduniwien.ac.at
Scientific contact	Prof. Werner Scheithauer, Medizinische Universität Wien, werner.scheithauer@meduniwien.ac.at
Sponsor organisation name	PrECOG, LLC
Sponsor organisation address	1818 Market Street, Suite 1100, Philadelphia, United States, PA 19103
Public contact	Project Manager, PrECOG LLC, candrews@precogllc.org
Scientific contact	Project Manager, PrECOG LLC, candrews@precogllc.org
Sponsor organisation name	Cancer Trials Ireland
Sponsor organisation address	RCSI House, 121 St. Stephen's Green, Dublin, Ireland, D02 H903
Public contact	Clinical Project Manager, Cancer Trials Ireland, info@cancertrials.ie
Scientific contact	Clinical Project Manager, Cancer Trials Ireland, info@cancertrials.ie

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 October 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 September 2016
Global end of trial reached?	Yes
Global end of trial date	01 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy of gemcitabine and nab-paclitaxel in patients with advanced CCA as measured by improvement in 6-month Progression Free Survival .

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy:

N/A

Evidence for comparator:

N/A The purpose of this study is to evaluate the effectiveness and safety of the combination of nab-paclitaxel and gemcitabine.

Actual start date of recruitment	17 September 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	United States: 71
Country: Number of subjects enrolled	Austria: 3
Worldwide total number of subjects	74
EEA total number of subjects	3

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)	44
From 65 to 84 years	28
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Seventy-four patients were enrolled at 23 community and academic centers across the United States and Europe between September 2014 and March 2016

Pre-assignment

Screening details:

The tartget population are patients with advanced or metastatic cholangiocarcinoma (CCA) who are not eligible for curative surgery, transplantation, or ablative therapies. They must meet all of the inclusion criteria and none of the exclusion criteria.

Pre-assignment period milestones

Number of subjects started	74
Number of subjects completed	73

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Inleigible: 1

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

N/A

Arms

Arm title	Single arm (Overall Trial)

Arm description:

Nab-Paclitaxel 125 mg/m² IV and Gemcitabine 1000 mg/m² on days 1, 8 and 15 every 28 days until progression or unacceptable toxicity.
Nab-Paclitaxel and Gemcitabine: Nab-Paclitaxel will be administered first, at a dose of 125 mg/m² IV over a period of 30 minutes; gemcitabine will be administered second, at a dose of 1000 mg/m² over a period of 30 minutes.

Arm type	Experimental
Investigational medicinal product name	nab-Paclitaxel
Investigational medicinal product code	
Other name	Abraxane
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Nab-Paclitaxel will be administered first, at a dose of 125 mg/m² IV over a period of 30 minutes.

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 will be administered second, at a dose of 1000 mg/m² over a period of 30 minutes.

Number of subjects in period 1[1]	Single arm (Overall Trial)
Started	73
Completed	2
Not completed	71
Physician decision	8
Consent withdrawn by subject	5
Adverse event, non-fatal	17
Max number of dose reduction	1
Death	2
Treatment delayed >4 weeks	3
Symptomatic progression	1
Patient opted to proceed to surgery	1
Lack of efficacy	33

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 74 Patients were enrolled but there was only 73 patients eligible and treated.

Baseline characteristics

Reporting groups	
Reporting group title	Single arm (Overall Trial)
Reporting group description:	
Nab-Paclitaxel 125 mg/m² IV and Gemcitabine 1000 mg/m² on days 1, 8 and 15 every 28 days until progression or unacceptable toxicity. Nab-Paclitaxel and Gemcitabine: Nab-Paclitaxel will be administered first, at a dose of 125 mg/m² IV over a period of 30 minutes; gemcitabine will be administered second, at a dose of 1000 mg/m² over a period of 30 minutes.	

Reporting group values	Single arm (Overall Trial)	Total	
Number of subjects	73	73	
Age categorical			
Eligible and treated patients			
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)	44	44	
From 65-84 years	28	28	
85 years and over	1	1	
Age continuous			
Units: years			
median	62		
full range (min-max)	36 to 87	-	
Gender categorical			
Units: Subjects			
Female	43	43	
Male	30	30	
Ethnicity			
Units: Subjects			
Hispanic or Latino	1	1	
Not Hispanic or Latino	71	71	
Unknown or Not Reported	1	1	
Race			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	1	1	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	3	3	
White	67	67	
More than one race	0	0	
Unknown or Not Reported	2	2	

Subject analysis sets

Subject analysis set title	Overall Trial
Subject analysis set type	Full analysis

Subject analysis set description:

This analysis set has been created as a workaround for reporting statistical analysis on a single arm study.

Reporting group values	Overall Trial		
Number of subjects	73		
Age categorical			
Eligible and treated patients			
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)	44		
From 65-84 years	28		
85 years and over	2		
Age continuous			
Units: years			
median	62		
full range (min-max)	36 to 87		
Gender categorical			
Units: Subjects			
Female	43		
Male	30		
Ethnicity			
Units: Subjects			
Hispanic or Latino	1		
Not Hispanic or Latino	71		
Unknown or Not Reported	1		
Race			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	1		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	3		
White	67		
More than one race	0		
Unknown or Not Reported	2		

End points

End points reporting groups

Reporting group title	Single arm (Overall Trial)

Reporting group description:

Nab-Paclitaxel 125 mg/m² IV and Gemcitabine 1000 mg/m² on days 1, 8 and 15 every 28 days until progression or unacceptable toxicity.
Nab-Paclitaxel and Gemcitabine: Nab-Paclitaxel will be administered first, at a dose of 125 mg/m² IV over a period of 30 minutes; gemcitabine will be administered second, at a dose of 1000 mg/m² over a period of 30 minutes.

Subject analysis set title	Overall Trial
Subject analysis set type	Full analysis

Subject analysis set description:

This analysis set has been created as a workaround for reporting statistical analysis on a single arm study.

Primary: Progression-Free Survival (PFS) Rate at 6 Months (Proportion of Participants Alive and Progression-Free at 6 Months)

End point title	Progression-Free Survival (PFS) Rate at 6 Months (Proportion of Participants Alive and Progression-Free at 6 Months)[1]

End point description:

Progression-free survival is defined as the time from the date of first study treatment to either the date of documented disease progression or death from any cause, whichever occurred first. Progression-free survival rate at 6 months is defined as the proportion of patients who were disease progression-free and alive at 6 months.

Progression is defined using Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.1), as a 20% increase in the sum of the diameter/axes of target lesions, taking as reference the smallest sum on study, or unequivocal progression of existing non-target lesions, or the appearance of new lesions.

End point type	Primary

End point timeframe:

Assessed at 6 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a single arm study with no comparison groups therefore statistical analyses (comparison analysis) were not conducted.

End point values	Single arm (Overall Trial)			
Subject group type	Reporting group			
Number of subjects analysed	73[2]			
Units: Proportion of participants				
number (confidence interval 95%)	0.605 (0.482 to 0.729)			

Notes:

[2] - Eligible and treated patients

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is defined as the time from enrollment until death or last patient contact.

End point type	Secondary

End point timeframe:

Every 3-6 months for up to 3 years

End point values	Single arm (Overall Trial)			
Subject group type	Reporting group			
Number of subjects analysed	73[3]			
Units: Months				
median (confidence interval 95%)	11.2 (9.6 to 14.7)			

Notes:

[3] - Eligible and treated patients

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)

End point description:

Progression-free survival is defined as the time from the date of first study treatment to either the date of documented disease progression or death from any cause, whichever occurred first.

End point type	Secondary

End point timeframe:

Every 3-6 months for up to 3 years

End point values	Single arm (Overall Trial)			
Subject group type	Reporting group			
Number of subjects analysed	73[4]			
Units: Months				
median (confidence interval 95%)	7.7 (5.9 to 13.1)			

Notes:

[4] - Eligible and treated patients

Statistical analyses

No statistical analyses for this end point

Secondary: Time To Progression (TTP)

End point title	Time To Progression (TTP)

End point description:

TTP was defined as the time from date of first dose of study therapy to date of removal from study for progression. Patients who have not experienced progression were censored at the date of last disease evaluation. Progression is evaluated using Solid Tumor Response Criteria (RECIST) Version 1.1. Progression is defined as at least a 20% increase in the sum of the diameters/axes of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm over the nadir. The appearance of new lesions or unequivocal progression of existing non-target lesions also constitutes disease progression.

End point type	Secondary

End point timeframe:

Every 3-6 months for up to 3 years

End point values	Single arm (Overall Trial)			
Subject group type	Reporting group			
Number of subjects analysed	73[5]			
Units: Months				
median (confidence interval 95%)	7.7 (6.5 to 13.1)			

Notes:

[5] - Eligible and treated

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)

End point description:

Overall response rate is defined as the proportion of patients with complete response or partial response per RECIST version 1.1. Complete response is defined as disappearance of all lesions. Partial response is defined as at least a 30% decrease in the sum of the diameters/axes of target lesions and the persistence of one or more non-target lesion(s) and/or the maintenance of tumor marker levels above the normal limits. A confirmation assessment performed >=4 weeks after the criteria for response is met is required.

End point type	Secondary

End point timeframe:

Every 3-6 months for up to 3 years

End point values	Single arm (Overall Trial)			
Subject group type	Reporting group			
Number of subjects analysed	73[6]			
Units: Proportion of participants				
number (confidence interval 95%)	0.301 (0.199 to 0.420)			

Notes:

[6] - Eligible and treated

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)

End point description:

Disease control rate is the proportion of patients achieved complete response, partial response or stable disease per RECIST version 1.1. Complete response is defined as disappearance of all lesions. Partial response is defined as at least a 30% decrease in the sum of the diameters/axes of target lesions and the persistence of one or more non-target lesion(s) and/or the maintenance of tumor marker levels above the normal limits. Stable disease is defined as neither sufficient shrinkage to qualify for complete or partial response nor sufficient increase to qualify for progression. A confirmation assessment performed >=4 weeks after the criteria for response is met is required.

End point type	Secondary

End point timeframe:

Every 3-6 months for up to 3 years

End point values	Single arm (Overall Trial)			
Subject group type	Reporting group			
Number of subjects analysed	73[7]			
Units: Proportion of participants				
number (confidence interval 95%)	0.658 (0.537 to 0.765)			

Notes:

[7] - Eligible and treated patients

Statistical analyses

No statistical analyses for this end point

Secondary: Association Between PFS and Maximum Change in Carbohydrate Antigen (CA) 19-9 From Baseline

End point title	Association Between PFS and Maximum Change in Carbohydrate Antigen (CA) 19-9 From Baseline

End point description:

Patients were dichotomized into maximum CA 19-9 decline >=50% and maximum CA 19-9 decline <50%. Cox proportional hazards model was used to evaluate the association between PFS and maximum change in CA 19-9.

End point type	Secondary

End point timeframe:

CA 19-9 was evaluated every 8 weeks until progression or for up to 3 years and off-treatment

End point values	Single arm (Overall Trial)	Overall Trial		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	35[8]	35[9]		
Units: Months				
number (confidence interval 95%)				
CA 19-9 decline >=50% (26 Participants)	7.7 (6.6 to 13.1)	7.7 (6.6 to 13.1)		
CA 19-9 decline <50% (9 Participants)	1.9 (1.6 to 18.2)	1.9 (1.6 to 18.2)		

Notes:

[8] - Eligible and treated patients with CA 19-9 data available

[9] - Eligible and treated patients with CA 19-9 data available

Statistical analyses

Statistical analysis title	Nab-Paclitaxel and Gemcitabine
Comparison groups	Single arm (Overall Trial) v Overall Trial
Number of subjects included in analysis	70
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.099
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	2.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	4.75

Secondary: Association Between OS and Maximum Change in Carbohydrate Antigen (CA) 19-9 From Baseline

End point title	Association Between OS and Maximum Change in Carbohydrate Antigen (CA) 19-9 From Baseline

End point description:

Patients were dichotomized into maximum CA 19-9 decline >=50% and maximum CA 19-9 decline <50%. Cox proportional hazards model was used to evaluate the association between OS and maximum change in CA 19-9.
The upper limit of the 95% confidence interval was not calculable because an insufficient number of participants reached the event at the final time point for assessment.

End point type	Secondary

End point timeframe:

CA 19-9 was evaluated every 8 weeks until progression or for up to 3 years and off-treatment

End point values	Single arm (Overall Trial)	Overall Trial		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	35[10]	35		
Units: Months				
number (not applicable)	35	35		

Notes:

[10] - Eligible and treated patients with CA 19-9 data available

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Circulating Tumor Cells (CTCs)

End point title	Change in Circulating Tumor Cells (CTCs)

End point description:

Correlate change in CTCs to median PFS, OS, TTP, ORR and DCR.

End point type	Secondary

End point timeframe:

Prior to Cycle 1, Day 1; Cycle 1 Day 8; Cycle 3, Day 1 and at Off Treatment

End point values	Single arm (Overall Trial)	Overall Trial		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	0[11]	0[12]		
Units: Outcome Measure Data Not Reported				
number (not applicable)				

Notes:

[11] - Outcome Measure Data Not Reported

[12] - Outcome Measure Data Not Reported

Statistical analyses

No statistical analyses for this end point

Secondary: Stromal SPARC Expression

End point title	Stromal SPARC Expression

End point description:

Correlate stromal SPARC (high versus low) expression by immunohistochemistry (IHC) with median PFS, OS, TTP, ORR and DCR.

End point type	Secondary

End point timeframe:

Baseline

End point values	Single arm (Overall Trial)	Overall Trial		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	0[13]	0[14]		
Units: Outcome Measure Data Not Reported				
number (not applicable)				

Notes:

[13] - Outcome Measure Data Not Reported

[14] - Outcome Measure Data Not Reported

Statistical analyses

No statistical analyses for this end point

Secondary: Fibrosis Expression

End point title	Fibrosis Expression

End point description:

Correlate fibrosis (low, intermediate and high) by trichrome staining with median PFS, OS, TTP, ORR and DCR.

End point type	Secondary

End point timeframe:

Baseline

End point values	Single arm (Overall Trial)	Overall Trial		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	0[15]	0[16]		
Units: Outcome Measure Data Not Reported				
number (not applicable)				

Notes:

[15] - Outcome Measure Data Not Reported

[16] - Outcome Measure Data Not Reported

Statistical analyses

No statistical analyses for this end point

Secondary: CDA Expression

End point title	CDA Expression

End point description:

Correlate CDA (high versus low) expression by IHC with median PFS, OS, TTP, ORR and DCR.

End point type	Secondary

End point timeframe:

Baseline

End point values	Single arm (Overall Trial)	Overall Trial		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	0[17]	0[18]		
Units: Outcome Measure Data Not Reported				
number (not applicable)				

Notes:

[17] - Outcome Measure Data Not Reported

[18] - Outcome Measure Data Not Reported

Statistical analyses

No statistical analyses for this end point

Secondary: hENT Expression

End point title	hENT Expression

End point description:

Correlate hENT1 (high versus low) expression by IHC with median PFS, OS, TTP, ORR and DCR.

End point type	Secondary

End point timeframe:

Baseline

End point values	Single arm (Overall Trial)	Overall Trial		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	0[19]	0[20]		
Units: Outcome Measure Data Not Reported				
number (not applicable)				

Notes:

[19] - Outcome Measure Data Not Reported

[20] - Outcome Measure Data Not Reported

Statistical analyses

No statistical analyses for this end point

Secondary: Banking Biospecimens for Future Assessment

End point title	Banking Biospecimens for Future Assessment

End point description:

Optional specimen banking of patient blood specimens (including serum, plasma and buffy coat) as well as fixed left-over tissue specimens when available from all enrolled patients in this trial for possible future molecular, pharmacogenomic, and/or proteomic testing.

End point type	Secondary

End point timeframe:

Prior to Cycle 1, Day 1; Cycle 1, Day 8; Cycle 3, Day 1 and at Off Treatment

End point values	Single arm (Overall Trial)	Overall Trial		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	0[21]	0[22]		
Units: Outcome Measure Data Not Reported				
number (not applicable)				

Notes:

[21] - Outcome Measure Data Not Reported

[22] - Outcome Measure Data Not Reported

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Assessed every week for the first 2 cycles, then every two cycles (every 8 weeks) and 30 days after the last dose of therapy

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Single arm (Overall Trial)

Reporting group description:

Nab-Paclitaxel 125 mg/m² IV and Gemcitabine 1000 mg/m² on days 1, 8 and 15 every 28 days until progression or unacceptable toxicity.
Nab-Paclitaxel and Gemcitabine: Nab-Paclitaxel will be administered first, at a dose of 125 mg/m² IV over a period of 30 minutes; gemcitabine will be administered second, at a dose of 1000 mg/m² over a period of 30 minutes.

Serious adverse events	Single arm (Overall Trial)		
Total subjects affected by serious adverse events			
subjects affected / exposed	42 / 74 (56.76%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	3 / 74 (4.05%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Embolism			
subjects affected / exposed	3 / 74 (4.05%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypotension			

subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombosis				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pregnancy, puerperium and perinatal conditions				
Headache				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Disease progression				
subjects affected / exposed	2 / 74 (2.70%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Generalised oedema				
subjects affected / exposed	2 / 74 (2.70%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Multi-organ failure				
subjects affected / exposed	2 / 74 (2.70%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Pyrexia			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences causally related to treatment / all	2 / 6		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Dyspnoea			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	2 / 74 (2.70%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Investigations			
Neutrophil count decreased			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Humerus fracture			

subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post procedural haemorrhage			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 74 (2.70%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pericardial effusion			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Tachycardia			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Facial nerve disorder			

subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhage intracranial				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic encephalopathy				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	2 / 74 (2.70%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Haemolytic uraemic syndromeemaly				
subjects affected / exposed	3 / 74 (4.05%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				

Abdominal pain				
subjects affected / exposed	3 / 74 (4.05%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	2 / 74 (2.70%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	3 / 74 (4.05%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Bile duct obstruction				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bile duct stenosis				
subjects affected / exposed	2 / 74 (2.70%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Biliary fistula				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Cholangitis				

subjects affected / exposed	3 / 74 (4.05%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholestasis				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperbilirubinaemia				
subjects affected / exposed	3 / 74 (4.05%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Rash macular				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Rash maculo-papular				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	2 / 74 (2.70%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				

Abscess				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Biliary tract infection				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile infection				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	2 / 74 (2.70%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Emphysematous cholecystitis				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenic sepsis				

subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypovolaemia			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Single arm (Overall Trial)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	72 / 74 (97.30%)		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	5		
Embolism			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	44		
Hot flashes			

subjects affected / exposed	6 / 74 (8.11%)		
occurrences (all)	6		
Hypertension			
subjects affected / exposed	10 / 74 (13.51%)		
occurrences (all)	10		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	5		
Chills			
subjects affected / exposed	11 / 74 (14.86%)		
occurrences (all)	11		
Fatigue			
subjects affected / exposed	53 / 74 (71.62%)		
occurrences (all)	53		
Influenza like illness			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	4		
Oedema peripheral			
subjects affected / exposed	31 / 74 (41.89%)		
occurrences (all)	31		
Pain			
subjects affected / exposed	7 / 74 (9.46%)		
occurrences (all)	7		
Pyrexia			
subjects affected / exposed	18 / 74 (24.32%)		
occurrences (all)	18		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 74 (14.86%)		
occurrences (all)	11		
Dyspnoea			
subjects affected / exposed	22 / 74 (29.73%)		
occurrences (all)	22		
Epistaxis			

subjects affected / exposed	11 / 74 (14.86%)		
occurrences (all)	11		
Pleural effusion			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	4		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	12 / 74 (16.22%)		
occurrences (all)	12		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	18 / 74 (24.32%)		
occurrences (all)	18		
Aspartate aminotransferase increased			
subjects affected / exposed	18 / 74 (24.32%)		
occurrences (all)	18		
Blood alkaline phosphatase increased			
subjects affected / exposed	17 / 74 (22.97%)		
occurrences (all)	17		
Blood bilirubin increased			
subjects affected / exposed	7 / 74 (9.46%)		
occurrences (all)	7		
Hyperbilirubinaemia			
subjects affected / exposed	7 / 74 (9.46%)		
occurrences (all)	7		
Hypoalbuminaemia			
subjects affected / exposed	9 / 74 (12.16%)		
occurrences (all)	9		
Hypocalcaemia			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	4		
Leukopenia			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	5		
Neutrophil count decreased			

subjects affected / exposed	14 / 74 (18.92%)		
occurrences (all)	14		
Platelet count decreased			
subjects affected / exposed	11 / 74 (14.86%)		
occurrences (all)	11		
Thrombocytopenia			
subjects affected / exposed	16 / 74 (21.62%)		
occurrences (all)	16		
Weight decreased			
subjects affected / exposed	22 / 74 (29.73%)		
occurrences (all)	22		
Weight increased			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	5		
White blood cell count decreased			
subjects affected / exposed	10 / 74 (13.51%)		
occurrences (all)	10		
Hyponatraemia			
subjects affected / exposed	8 / 74 (10.81%)		
occurrences (all)	8		
Nervous system disorders			
Dizziness			
subjects affected / exposed	11 / 74 (14.86%)		
occurrences (all)	11		
Dysgeusia			
subjects affected / exposed	17 / 74 (22.97%)		
occurrences (all)	17		
Headache			
subjects affected / exposed	6 / 74 (8.11%)		
occurrences (all)	6		
Neuropathy peripheral			
subjects affected / exposed	28 / 74 (37.84%)		
occurrences (all)	28		
Peripheral sensory neuropathy			
subjects affected / exposed	9 / 74 (12.16%)		
occurrences (all)	9		

Tremor subjects affected / exposed occurrences (all)	4 / 74 (5.41%) 4		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all)	 31 / 74 (41.89%) 31 26 / 74 (35.14%) 26		
Eye disorders Vision blurred subjects affected / exposed occurrences (all)	 5 / 74 (6.76%) 5		
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) Ascites subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Decreased appetite subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dry mouth subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Stomatitis	 5 / 74 (6.76%) 5 5 / 74 (6.76%) 5 34 / 74 (45.95%) 34 28 / 74 (37.84%) 28 35 / 74 (47.30%) 35 4 / 74 (5.41%) 4 34 / 74 (45.95%) 34		

subjects affected / exposed occurrences (all)	8 / 74 (10.81%) 8		
Vomiting subjects affected / exposed occurrences (all)	18 / 74 (24.32%) 18		
Abdominal pain subjects affected / exposed occurrences (all)	12 / 74 (16.22%) 12		
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	39 / 74 (52.70%) 39		
Nail discolouration subjects affected / exposed occurrences (all)	5 / 74 (6.76%) 5		
Pruritus subjects affected / exposed occurrences (all)	5 / 74 (6.76%) 5		
Rash subjects affected / exposed occurrences (all)	9 / 74 (12.16%) 9		
Rash maculo-papular subjects affected / exposed occurrences (all)	7 / 74 (9.46%) 7		
Renal and urinary disorders			
Acute kidney injury subjects affected / exposed occurrences (all)	5 / 74 (6.76%) 5		
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	13 / 74 (17.57%) 13		
Back pain subjects affected / exposed occurrences (all)	6 / 74 (8.11%) 6		
Bone pain			

subjects affected / exposed occurrences (all)	4 / 74 (5.41%) 4		
Muscular weakness subjects affected / exposed occurrences (all)	14 / 74 (18.92%) 14		
Musculoskeletal pain subjects affected / exposed occurrences (all)	5 / 74 (6.76%) 5		
Myalgia subjects affected / exposed occurrences (all)	8 / 74 (10.81%) 8		
Pain in extremity subjects affected / exposed occurrences (all)	9 / 74 (12.16%) 9		
Infections and infestations Mucosal inflammation subjects affected / exposed occurrences (all)	4 / 74 (5.41%) 4		
Sepsis subjects affected / exposed occurrences (all)	4 / 74 (5.41%) 4		
Metabolism and nutrition disorders Dehydration subjects affected / exposed occurrences (all)	7 / 74 (9.46%) 7		
Hypokalaemia subjects affected / exposed occurrences (all)	7 / 74 (9.46%) 7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30178032