Clinical trial results:
Phase Ib-II study of Ramucirumab combined with standard Nab-paclitaxel and Gemcitabine as first-line treatment in patients with advanced pancreatic adenocarcinoma.

Summary

EudraCT number	2017-004792-30
Trial protocol	GR
Global end of trial date	23 April 2023

Results information

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

Trial information

Trial identification

Sponsor protocol code	HE316

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Hellenic Cooperative Oncology Group
Sponsor organisation address	41 Mesogeion Avenue, Athens, Greece, 115 26
Public contact	Clinical Trials, Hellenic Cooperative Oncology Group (HeCOG), 0030 2106912520, hecogoff@otenet.gr
Scientific contact	Clinical Trials, Hellenic Cooperative Oncology Group (HeCOG), 0030 2106912520, hecogoff@otenet.gr

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	18 April 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 April 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- Phase Ib: The safety of the combination of Nab-paclitaxel - Gemcitabine with Ramucirumab in 4-weekly cycles by determining the Recommended Dose (RD) during the first two cycles of therapy (8 weeks).
- Phase II: Efficacy by determination of the objective response rate (ORR) by RECIST criteria of the combination of Ramucirumab with Nab-paclitaxel and Gemcitabine administered in 4-weekly cycles.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial. A copy of the IEC/IRB approval was received by the sponsor before recruitment of subjects into the study and all subjects provided written informed consent before undergoing any study-related procedures.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 January 2019
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	Greece: 54
Worldwide total number of subjects	54
EEA total number of subjects	54

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)	19
From 65 to 84 years	35
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled in the study from 29 January 2019 until 18 October 2021 from 11 sites in Greece.

Pre-assignment

Screening details:

Patients signed the informed consent form and were screened for eligibility before entering the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase Ib

Arm description:

The first 12 patients entered the phase Ib study in 2 cohorts of 6 patients each. In the first cohort, six patients started Ramucirumab followed by Nab-paclitaxel and Gemcitabine every 4 weeks for 2 cycles at the specific initial dose level. Modification of the initial dose depended on the frequency of dose limiting toxicities (DLT) and followed specific rules. When the dose was determined in the first cohort, then the second cohort was enrolled to test the safety of this dose. The Phase II Recommended dose (RD) for the phase II part of the study was determined when all 6+6 patients completed a maximum of 2 cycles. In the screening period, 1 patient had a SAE once ICF was signed and was monitored for safety reasons. Patient did not receive any intervention and was set off study protocol. During phase Ib 2 patients were found ineligible they had received at least 1 cycle of therapy and had to be replaced since the Recommended Dose had to be determined in 12 eligible patients.

Arm type	Experimental
Investigational medicinal product name	Ramucirumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose Level 0 Ramucirumab 8mg/kg
Dose Level -1 Ramucirumab 8mg/kg

Arm title	Phase II

Arm description:

In the phase II part of the trial, new patients were recruited and started the study treatment according to the RD determined at the second cohort of the phase Ib part. Phase Ib patients entered the phase II part by continuing the treatment beyond the second cycle at the RD level. The first cohort of the phase Ib part entered the phase II part by continuing the treatment beyond the second cycle at the dose level determined at this cohort. Dose reductions in the phase II study followed the standards according to the drugs' Summary of Product Characteristics (SPCs). One patient was not included in the analysis due to consent withdrawal prior to receiving any treatment and no SAE was reported.

Arm type	Experimental

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

Dosage and administration details:

Ramucirumab 10mg/kg was the recomended dose for the Phase II study.

Number of subjects in period 1	Phase Ib	Phase II
Started	15	39
Completed	11	9
Not completed	4	30
Adverse event, serious fatal	1	4
Consent withdrawn by subject	-	2
Physician decision	-	1
Disease progression	1	13
Adverse event, non-fatal	-	5
Death	-	2
Protocol deviation	2	-
Off treatment more than 2 weeks	-	3

Baseline characteristics

Reporting groups	
Reporting group title	Phase Ib

Reporting group description:

The first 12 patients entered the phase Ib study in 2 cohorts of 6 patients each. In the first cohort, six patients started Ramucirumab followed by Nab-paclitaxel and Gemcitabine every 4 weeks for 2 cycles at the specific initial dose level. Modification of the initial dose depended on the frequency of dose limiting toxicities (DLT) and followed specific rules. When the dose was determined in the first cohort, then the second cohort was enrolled to test the safety of this dose. The Phase II Recommended dose (RD) for the phase II part of the study was determined when all 6+6 patients completed a maximum of 2 cycles. In the screening period, 1 patient had a SAE once ICF was signed and was monitored for safety reasons. Patient did not receive any intervention and was set off study protocol. During phase Ib 2 patients were found ineligible they had received at least 1 cycle of therapy and had to be replaced since the Recommended Dose had to be determined in 12 eligible patients.

Reporting group title	Phase II

Reporting group description:

In the phase II part of the trial, new patients were recruited and started the study treatment according to the RD determined at the second cohort of the phase Ib part. Phase Ib patients entered the phase II part by continuing the treatment beyond the second cycle at the RD level. The first cohort of the phase Ib part entered the phase II part by continuing the treatment beyond the second cycle at the dose level determined at this cohort. Dose reductions in the phase II study followed the standards according to the drugs' Summary of Product Characteristics (SPCs). One patient was not included in the analysis due to consent withdrawal prior to receiving any treatment and no SAE was reported.

Reporting group values	Phase Ib	Phase II	Total
Number of subjects	15	39	54
Age categorical Units: Subjects			
Adults (18-64 years)	8	11	19
From 65-84 years	7	28	35
Age continuous Units: years			
median	63.4	69.5	
full range (min-max)	44.8 to 80	40.4 to 76	-
Gender categorical Units: Subjects			
Female	8	18	26
Male	7	21	28

End points

End points reporting groups

Reporting group title	Phase Ib

Reporting group description:

The first 12 patients entered the phase Ib study in 2 cohorts of 6 patients each. In the first cohort, six patients started Ramucirumab followed by Nab-paclitaxel and Gemcitabine every 4 weeks for 2 cycles at the specific initial dose level. Modification of the initial dose depended on the frequency of dose limiting toxicities (DLT) and followed specific rules. When the dose was determined in the first cohort, then the second cohort was enrolled to test the safety of this dose. The Phase II Recommended dose (RD) for the phase II part of the study was determined when all 6+6 patients completed a maximum of 2 cycles. In the screening period, 1 patient had a SAE once ICF was signed and was monitored for safety reasons. Patient did not receive any intervention and was set off study protocol. During phase Ib 2 patients were found ineligible they had received at least 1 cycle of therapy and had to be replaced since the Recommended Dose had to be determined in 12 eligible patients.

Reporting group title	Phase II

Reporting group description:

In the phase II part of the trial, new patients were recruited and started the study treatment according to the RD determined at the second cohort of the phase Ib part. Phase Ib patients entered the phase II part by continuing the treatment beyond the second cycle at the RD level. The first cohort of the phase Ib part entered the phase II part by continuing the treatment beyond the second cycle at the dose level determined at this cohort. Dose reductions in the phase II study followed the standards according to the drugs' Summary of Product Characteristics (SPCs). One patient was not included in the analysis due to consent withdrawal prior to receiving any treatment and no SAE was reported.

Primary: Safety of the combination of Ramucirumab with Nab-paclitaxel and Gemcitabine

End point title	Safety of the combination of Ramucirumab with Nab-paclitaxel and Gemcitabine[1][2]

End point description:

One-to-two cohorts of 6 patients each will receive two cycles of the regimen at active dose levels. The final dose will be determined according to a specific algorithm described in the protocol.

End point type	Primary

End point timeframe:

From study initiation until the determination of the Recommended Dose (RD) during the first two cycles of therapy (8 weeks).

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The determination of the maximum tolerated dose of Ramucirumab with Nab-paclitaxel and Gemcitabine was the primary endpoint of the Phase Ib part of the study. Gemcitabine doses per dose level are described for patients enrolled in the Phase Ib part of the study.
[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: Since this was a single arm Phase Ib/II trial and all patients were treated with Ramucirumab,Nab-paclitaxel and Gemcitabine, no comparisons between different treatment arms were performed. The number of patients evaluable for DLT per dose level is described for patients enrolled in the Phase Ib part of the study.

End point values	Phase Ib			
Subject group type	Reporting group			
Number of subjects analysed	15[3]			
Units: Number of patients evaluable for DLT				
Dose Level 0 Gemcitabine 1000 mg/m2	6			

Dose Level -1 Gemcitabine 800 mg/m2	6			

Notes:

[3] - One patient did not start treatment and two were found ineligible.

Statistical analyses

No statistical analyses for this end point

Primary: Overall Response rate (ORR)

End point title	Overall Response rate (ORR)[4][5]

End point description:

ORR is defined as the proportion of patients with confirmed Complete Response (CR) or confirmed Partial Response (PR) as best overall response to treatment, based on Response Evaluation Criteria in Solid Tumors (RECIST) v. 1.1 guidelines .

End point type	Primary

End point timeframe:

CT or MRI scan performed to assess disease status at baseline and every 8 weeks from the start of study treatment for the first 8months of study treatment, then every 12 weeks, or until disease progression.

Notes:

[4] - 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: Since this was a single arm Phase Ib/II trial and all patients were treated with Ramucirumab, Nab-paclitaxel and Gemcitabine no comparisons between different treatment arms were performed. The percentage of patients surviving 6 months since study entry has been provided for the patients included in the Phase II part of the study.
[5] - 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: Since this was a single arm Phase Ib/II trial and all patients were treated with Ramucirumab, Nab-paclitaxel and Gemcitabine no comparisons between different treatment arms were performed. The 6-month Overall Response rate was the primary endpoint of the Phase II part of the study. The percentage of Phase II patients surviving 6 months since study entry is described.

End point values	Phase II			
Subject group type	Reporting group			
Number of subjects analysed	38[6]			
Units: months				
median (confidence interval 95%)	9.9 (5.4 to 15)			

Notes:

[6] - 1 patient withdrew consent prior to receiving any treatment and no SAE was reported.

Attachments (see zip file)	Kaplan - Meier for DOR/Kaplan-Meier for DOR.tif

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

End point type	Secondary

End point timeframe:

Overall survival is defined as the time interval from registration to the date of death due to any cause or last contact.

End point values	Phase Ib	Phase II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15[7]	38[8]		
Units: months				
median (confidence interval 95%)	14 (7.3 to 18)	14 (7.3 to 18)		

Notes:

[7] - OS endpoint was collectively estimated for both Phase Ib and Phase II.

[8] - 1 patient withdrew consent prior to receiving any treatment and no SAE was reported.

Attachments (see zip file)	Kaplan - Meier for Overall Survival/Kaplan - Meier for Overall

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

End point type	Secondary

End point timeframe:

PFS is defined as the time interval from registration to the first date of documented tumor progression, death from any cause or last contact.

End point values	Phase Ib	Phase II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15[9]	38[10]		
Units: months				
median (confidence interval 95%)	4 (4 to 10)	4 (4 to 10)		

Notes:

[9] - PFS endpoint was collectively estimated for both Phase Ib and Phase II.

[10] - 1 patient withdrew consent prior to receiving any treatment and no SAE was reported.

Attachments (see zip file)	Kaplan - Meier for PFS/Kaplan - Meier for PFS.png

Statistical analyses

No statistical analyses for this end point

Secondary: Safety

End point title	Safety

End point description:

Safety was recorded for the nab-paclitaxel – gemcitabine – ramucirumab treatment part as well during the maintenance therapy.

End point type	Secondary

End point timeframe:

Adverse event data, vital signs and laboratory data of all patients were recorded and assessed upon signature of the inform consent until 30 days after the last administration of study treatment.

End point values	Phase Ib	Phase II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	38[11]		
Units: Number of patients analysed				
Any Adverse Event	15	37		
Fatal Adverse Events	1	5		
Serious Adverse Events	10	10		

Notes:

[11] - 1 patient withdrew consent prior to receiving any treatment and no SAE was reported.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Upon signature of the the informed consent form up to 30 days after the last administration of any investigational product.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	9.1

Reporting groups

Reporting group title	Phase Ib

Reporting group description:

The first 12 patients entered the phase Ib study in 2 cohorts of 6 patients each. In the first cohort, six patients started Ramucirumab followed by Nab-paclitaxel and Gemcitabine every 4 weeks for 2 cycles at the specific initial dose level. Modification of the initial dose depended on the frequency of dose limiting toxicities (DLT) and followed specific rules. When the dose was determined in the first cohort, then the second cohort was enrolled to test the safety of this dose. For the second cohort, the same dose modification rules according to the occurrence of DLT was followed. The Phase II Recommended dose (RD) for the phase II part of the study was determined when all 6+6 patients completed a maximum of 2 cycles.

Reporting group title	Phase II

Reporting group description:

In the phase II part of the trial, new patients were recruited and started the study treatment according to the RD determined at the second cohort of the phase Ib part. Phase Ib patients entered the phase II part by continuing the treatment beyond the second cycle at the RD level. The first cohort of the phase Ib part entered the phase II part by continuing the treatment beyond the second cycle at the dose level determined at this cohort. Dose reductions in the phase II study followed the standards according to the drugs' Summary of Product Characteristics (SPCs).

Serious adverse events	Phase Ib	Phase II	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 14 (64.29%)	10 / 38 (26.32%)	
number of deaths (all causes)	1	5	
number of deaths resulting from adverse events			
Investigations			
Creatinine increased			
subjects affected / exposed	0 / 14 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Thromboembolic event			
subjects affected / exposed	0 / 14 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	

Vascular disorders - Other, specify - Mesenterium thrombosis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 14 (7.14%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stroke			
subjects affected / exposed	1 / 14 (7.14%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	0 / 14 (0.00%)	2 / 38 (5.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Edema limbs			
subjects affected / exposed	0 / 14 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever			
subjects affected / exposed	2 / 14 (14.29%)	2 / 38 (5.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death NOS			
subjects affected / exposed	0 / 14 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 14 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric hemorrhage			
subjects affected / exposed	0 / 14 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ileus			
subjects affected / exposed	0 / 14 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pancreatic fistula			
subjects affected / exposed	0 / 14 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Portal vein thrombosis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders - Other, specify - Febrile Cholangitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders - Other, specify - Liver absesses			
subjects affected / exposed	1 / 14 (7.14%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders - Other, specify - Cholangitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatobiliary disorders - Other, specify - Billiary Obstruction			
subjects affected / exposed	1 / 14 (7.14%)	0 / 38 (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			
Dyspnea			
subjects affected / exposed	0 / 14 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anorectal infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infections and infestations - Other, specify - Infection Pseudomonas			
subjects affected / exposed	1 / 14 (7.14%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations - Other, specify - Covid19			
subjects affected / exposed	0 / 14 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations - Other, specify - Bacteremia -			
subjects affected / exposed	0 / 14 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations - Other, specify - Perianal abscess			

subjects affected / exposed	1 / 14 (7.14%)	0 / 38 (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			
Metabolism and nutrition disorders - Other, specify - Hyperbilirubinemia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Phase Ib	Phase II	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 14 (85.71%)	37 / 38 (97.37%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 14 (35.71%)	17 / 38 (44.74%)	
occurrences (all)	9	41	
Alkaline phosphatase increased			
subjects affected / exposed	3 / 14 (21.43%)	13 / 38 (34.21%)	
occurrences (all)	5	26	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 14 (14.29%)	17 / 38 (44.74%)	
occurrences (all)	5	39	
Blood bilirubin increased			
subjects affected / exposed	0 / 14 (0.00%)	2 / 38 (5.26%)	
occurrences (all)	0	2	
Creatinine increased			
subjects affected / exposed	0 / 14 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
GGT increased			
subjects affected / exposed	2 / 14 (14.29%)	13 / 38 (34.21%)	
occurrences (all)	3	16	
Weight loss			

subjects affected / exposed	0 / 14 (0.00%)	2 / 38 (5.26%)	
occurrences (all)	0	2	
White blood cell decreased			
subjects affected / exposed	2 / 14 (14.29%)	15 / 38 (39.47%)	
occurrences (all)	5	42	
Platelet count decreased			
subjects affected / exposed	4 / 14 (28.57%)	22 / 38 (57.89%)	
occurrences (all)	9	93	
Neutrophil count decreased			
subjects affected / exposed	5 / 14 (35.71%)	19 / 38 (50.00%)	
occurrences (all)	9	53	
Lymphocyte count decreased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
INR increased			
subjects affected / exposed	0 / 14 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Investigations - Other, specify - LDH increased			
subjects affected / exposed	0 / 14 (0.00%)	5 / 38 (13.16%)	
occurrences (all)	0	15	
Investigations - Other, specify - Platelet count increased			
subjects affected / exposed	0 / 14 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 14 (7.14%)	6 / 38 (15.79%)	
occurrences (all)	1	6	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	0 / 14 (0.00%)	2 / 38 (5.26%)	
occurrences (all)	0	2	
Headache			
subjects affected / exposed	0 / 14 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Peripheral sensory neuropathy			

subjects affected / exposed	1 / 14 (7.14%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders - Other, specify - Sensory neurotoxicity			
subjects affected / exposed	0 / 14 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Nervous system disorders - Other, specify -Neuropathic pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Nervous system disorders - Other, specify -Numbness			
subjects affected / exposed	0 / 14 (0.00%)	2 / 38 (5.26%)	
occurrences (all)	0	2	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	5 / 14 (35.71%)	22 / 38 (57.89%)	
occurrences (all)	8	37	
General disorders and administration site conditions			
Edema limbs			
subjects affected / exposed	0 / 14 (0.00%)	5 / 38 (13.16%)	
occurrences (all)	0	5	
Fatigue			
subjects affected / exposed	5 / 14 (35.71%)	13 / 38 (34.21%)	
occurrences (all)	5	17	
Fever			
subjects affected / exposed	5 / 14 (35.71%)	5 / 38 (13.16%)	
occurrences (all)	11	10	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 14 (7.14%)	1 / 38 (2.63%)	
occurrences (all)	1	1	
Constipation			
subjects affected / exposed	0 / 14 (0.00%)	3 / 38 (7.89%)	
occurrences (all)	0	3	
Diarrhea			

subjects affected / exposed	1 / 14 (7.14%)	10 / 38 (26.32%)	
occurrences (all)	1	21	
Ileus			
subjects affected / exposed	0 / 14 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	2 / 14 (14.29%)	5 / 38 (13.16%)	
occurrences (all)	2	8	
Gastrointestinal disorders - Other, specify - Dental extraction			
subjects affected / exposed	0 / 14 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	2	
Gastrointestinal disorders - Other, specify - Dental abscess			
subjects affected / exposed	0 / 14 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Gastrointestinal disorders - Other, specify - Hemorrhagic diarrhea			
subjects affected / exposed	0 / 14 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	0 / 14 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Epistaxis			
subjects affected / exposed	0 / 14 (0.00%)	8 / 38 (21.05%)	
occurrences (all)	0	14	
Pneumothorax			
subjects affected / exposed	0 / 14 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 14 (7.14%)	5 / 38 (13.16%)	
occurrences (all)	1	5	
Rash acneiform			
subjects affected / exposed	0 / 14 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	

Renal and urinary disorders			
Hematuria			
subjects affected / exposed	0 / 14 (0.00%)	2 / 38 (5.26%)	
occurrences (all)	0	2	
Proteinuria			
subjects affected / exposed	0 / 14 (0.00%)	6 / 38 (15.79%)	
occurrences (all)	0	10	
Renal and urinary disorders - Other, specify - Microalbuminuria			
subjects affected / exposed	0 / 14 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Joint effusion			
subjects affected / exposed	0 / 14 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Infections and infestations - Other, specify - Covid19			
subjects affected / exposed	0 / 14 (0.00%)	2 / 38 (5.26%)	
occurrences (all)	0	2	
Infections and infestations - Other, specify - Furuncle			
subjects affected / exposed	0 / 14 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	0 / 14 (0.00%)	5 / 38 (13.16%)	
occurrences (all)	0	7	
Hypercalcaemia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Hyperglycemia			

subjects affected / exposed	2 / 14 (14.29%)	5 / 38 (13.16%)	
occurrences (all)	7	10	
Hyperkalemia			
subjects affected / exposed	1 / 14 (7.14%)	1 / 38 (2.63%)	
occurrences (all)	1	1	
Hypernatremia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	5	
Hyperuricemia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Hypoalbuminemia			
subjects affected / exposed	2 / 14 (14.29%)	14 / 38 (36.84%)	
occurrences (all)	2	23	
Hypocalcemia			
subjects affected / exposed	2 / 14 (14.29%)	10 / 38 (26.32%)	
occurrences (all)	2	11	
Hypoglycemia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Hypokalemia			
subjects affected / exposed	0 / 14 (0.00%)	3 / 38 (7.89%)	
occurrences (all)	0	5	
Hyponatremia			
subjects affected / exposed	0 / 14 (0.00%)	3 / 38 (7.89%)	
occurrences (all)	0	4	
Hypophosphatemia			
subjects affected / exposed	0 / 14 (0.00%)	2 / 38 (5.26%)	
occurrences (all)	0	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 July 2020	- Change of Coordinating Principal Investigator - Addition of Statistician and Safety Coordinator - Update of communication information

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

None reported

Notes: