Clinical trial results:
A Randomized, Multi-center, Double-blinded, Placebo-controlled Phase 3 Study of Nivolumab and Ipilimumab, Nivolumab Monotherapy, or Placebo in Combination with Trans-arterial ChemoEmbolization (TACE) in Patients with Intermediate-stage Hepatocellular Carcinoma (HCC)

Summary

EudraCT number	2019-002790-58
Trial protocol	AT FR DE BE CZ IT
Global end of trial date	23 December 2023

Results information

Result version number	v1 (current)
This version publication date	21 November 2024
First version publication date	21 November 2024

Trial information

Trial identification

Sponsor protocol code	CA209-74W

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04340193
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussee de la Hulpe 185, Brussels, Belgium, 1170
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com

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	12 December 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 December 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the safety and tolerability of nivolumab with and without ipilimumab in combination with Trans-arterial ChemoEmbolization (TACE) to TACE alone in participants with intermediate liver cancer.

Protection of trial subjects:

Patient Confidentiality, Personal Data Protection and Biomarker Consent

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 September 2020
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	Austria: 1
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Hong Kong: 2
Country: Number of subjects enrolled	Japan: 5
Country: Number of subjects enrolled	Korea, Republic of: 3
Country: Number of subjects enrolled	Russian Federation: 1
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Taiwan: 4
Country: Number of subjects enrolled	United States: 1
Worldwide total number of subjects	26
EEA total number of subjects	10

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)	11
From 65 to 84 years	14
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted in Austria, Belgium, France, Germany, Hong Kong, Japan, Republic of Korea, Russian Federation, Spain, Taiwan and United States

Pre-assignment

Screening details:

Screening procedures occurred within 28 days prior to first dose.
Screening begins by establishing the participant's initial eligibility and signing of the ICF.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	NIVO+IPI+TACE

Arm description:

Participants with intermediate-stage hepatocellular carcinoma (HCC) received Nivolumab (NIVO) 240 milligram (mg) every 2 weeks (Q2W) and ipilimumab (IPI) 1 milligram per kilogram (mg/kg) every 6 weeks (Q6W) as an approximately 30-minute infusion. Participants received first Trans-arterial ChemoEmbolization (TACE) in 7 days after randomization and then TACE as needed, until participant was no longer eligible for further TACE, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.

Arm type	Experimental
Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	Opdivo BMS-936558
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

240 milligram (mg) every 2 weeks (Q2W)

Investigational medicinal product name	Trans-arterial ChemoEmbolization (TACE)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for emulsion for infusion
Routes of administration	Intraarterial use

Dosage and administration details:

Inject the emulsion of the anticancer agent(s); Embolize the feeding artery with an embolization agent (eg, gelatin sponge); Inject Drug Eluting Beads (DEB).

Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

1 milligram per kilogram (mg/kg) every 6 weeks (Q6W) as an approximately 30-minute infusion

Arm title	NIVO+TACE

Arm description:

Participants with intermediate-stage hepatocellular carcinoma (HCC) received Nivolumab 240 milligram (mg) every 2 weeks (Q2W) as an approximately 30-minute infusion. Participants received first Trans-arterial ChemoEmbolization (TACE) in 7 days after randomization and then TACE as needed, until participant was no longer eligible for further TACE, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.

Arm type	Experimental
Investigational medicinal product name	Trans-arterial ChemoEmbolization (TACE)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for emulsion for infusion
Routes of administration	Intraarterial use

Dosage and administration details:

Inject the emulsion of the anticancer agent(s); Embolize the feeding artery with an embolization agent (eg, gelatin sponge); Inject Drug Eluting Beads (DEB).

Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	Opdivo BMS-936558
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

240 milligram (mg) every 2 weeks (Q2W)

Arm title	TACE

Arm description:

Participants received first Trans-arterial ChemoEmbolization (TACE) in 7 days after randomization and then TACE as needed, until participant was no longer eligible for further TACE, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.

Arm type	Active comparator
Investigational medicinal product name	Trans-arterial ChemoEmbolization (TACE)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for emulsion for infusion
Routes of administration	Intraarterial use

Dosage and administration details:

Inject the emulsion of the anticancer agent(s); Embolize the feeding artery with an embolization agent (eg, gelatin sponge); Inject Drug Eluting Beads (DEB).

Number of subjects in period 1	NIVO+IPI+TACE	NIVO+TACE	TACE
Started	9	9	8
Completed	6	4	4
Not completed	3	5	4
Study drug toxicity	1	-	-
Adverse event, non-fatal	1	1	-
Other Reason	-	-	1
Disease Recurrence	-	1	-
Disease Progression	1	2	3
Administrative Reasons by Sponsor	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	NIVO+IPI+TACE
Reporting group description:	
Participants with intermediate-stage hepatocellular carcinoma (HCC) received Nivolumab (NIVO) 240 milligram (mg) every 2 weeks (Q2W) and ipilimumab (IPI) 1 milligram per kilogram (mg/kg) every 6 weeks (Q6W) as an approximately 30-minute infusion. Participants received first Trans-arterial ChemoEmbolization (TACE) in 7 days after randomization and then TACE as needed, until participant was no longer eligible for further TACE, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.	
Reporting group title	NIVO+TACE
Reporting group description:	
Participants with intermediate-stage hepatocellular carcinoma (HCC) received Nivolumab 240 milligram (mg) every 2 weeks (Q2W) as an approximately 30-minute infusion. Participants received first Trans-arterial ChemoEmbolization (TACE) in 7 days after randomization and then TACE as needed, until participant was no longer eligible for further TACE, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.	
Reporting group title	TACE
Reporting group description:	
Participants received first Trans-arterial ChemoEmbolization (TACE) in 7 days after randomization and then TACE as needed, until participant was no longer eligible for further TACE, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.	

Reporting group values	NIVO+IPI+TACE	NIVO+TACE	TACE
Number of subjects	9	9	8
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	3	6	2
From 65-84 years	5	3	6
85 years and over	1	0	0
Age Continuous Units: years			
arithmetic mean	72.3	62.7	70.3
standard deviation	± 10.28	± 11.19	± 8.89
Sex: Female, Male Units: participants			
Female	2	1	1
Male	7	8	7
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	1	0
Not Hispanic or Latino	0	4	4
Unknown or Not Reported	9	4	4
Race			

Units: Subjects			
White	3	3	2
Black or African American	0	1	0
Asian	0	1	3
Chinese	2	2	1
Japanese	2	1	2
Not Reported	2	1	0

Reporting group values	Total		
Number of subjects	26		
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)	11		
From 65-84 years	14		
85 years and over	1		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: participants			
Female	4		
Male	22		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1		
Not Hispanic or Latino	8		
Unknown or Not Reported	17		
Race Units: Subjects			
White	8		
Black or African American	1		
Asian	4		
Chinese	5		
Japanese	5		
Not Reported	3		

End points

End points reporting groups

Reporting group title	NIVO+IPI+TACE

Reporting group description:

Participants with intermediate-stage hepatocellular carcinoma (HCC) received Nivolumab (NIVO) 240 milligram (mg) every 2 weeks (Q2W) and ipilimumab (IPI) 1 milligram per kilogram (mg/kg) every 6 weeks (Q6W) as an approximately 30-minute infusion. Participants received first Trans-arterial ChemoEmbolization (TACE) in 7 days after randomization and then TACE as needed, until participant was no longer eligible for further TACE, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.

Reporting group title	NIVO+TACE

Reporting group description:

Participants with intermediate-stage hepatocellular carcinoma (HCC) received Nivolumab 240 milligram (mg) every 2 weeks (Q2W) as an approximately 30-minute infusion. Participants received first Trans-arterial ChemoEmbolization (TACE) in 7 days after randomization and then TACE as needed, until participant was no longer eligible for further TACE, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.

Reporting group title	TACE

Reporting group description:

Participants received first Trans-arterial ChemoEmbolization (TACE) in 7 days after randomization and then TACE as needed, until participant was no longer eligible for further TACE, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.

Primary: Number of Participants with Adverse Events

End point title	Number of Participants with Adverse Events[1]

End point description:

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment. All treated participants.

End point type	Primary

End point timeframe:

From first dose and 30 days after last dose of study therapy (up to approximately 25 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: Statistical comparison was not required as per study design

End point values	NIVO+IPI+TACE	NIVO+TACE	TACE	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	9	8	
Units: participants	9	9	8	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Serious Adverse Events (SAEs)

End point title	Number of Participants with Serious Adverse Events (SAEs)[2]

End point description:

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose that results in death, Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe) or requires inpatient hospitalization or causes prolongation of existing hospitalization, or results in persistent or significant disability/incapacity or is a congenital anomaly/birth defect or is an important medical event. All treated participants.

End point type	Primary

End point timeframe:

From first dose and 30 days after last dose of study therapy (up to approximately 25 months)

Notes:

[2] - 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: Statistical comparison was not required as per study design

End point values	NIVO+IPI+TACE	NIVO+TACE	TACE	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	9	8	
Units: participants	7	6	2	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants who Died

End point title	Number of Participants who Died[3]

End point description:

All treated participants

End point type	Primary

End point timeframe:

From first dose and 100 days after last dose of study therapy (up to approximately 27 months)

Notes:

[3] - 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: Statistical comparison was not required as per study design

End point values	NIVO+IPI+TACE	NIVO+TACE	TACE	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	9	8	
Units: participants	2	2	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Adverse Events Leading to Study Drug discontinuation

End point title	Number of Participants with Adverse Events Leading to Study

	Drug discontinuation[4]

End point description:

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment. All treated participants.

End point type	Primary

End point timeframe:

From first dose and 30 days after last dose of study therapy (up to approximately 25 months)

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: Statistical comparison was not required as per study design

End point values	NIVO+IPI+TACE	NIVO+TACE	TACE	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	9	8	
Units: participants	3	1	1	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Worst Grade (Grade 3/4) Laboratory Results

End point title	Number of Participants with Worst Grade (Grade 3/4) Laboratory Results[5]

End point description:

Laboratory results were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (Grade 3 =Severe, Grade 4 = Life-threatening). All treated participants. Highest grade measured for hemoglobin and albumin was Grade 3.

End point type	Primary

End point timeframe:

From first dose and 30 days after last dose of study therapy (up to approximately 25 months)

Notes:

[5] - 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: Statistical comparison was not required as per study design

End point values	NIVO+IPI+TACE	NIVO+TACE	TACE	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	9	8	
Units: participants				
Hemoglobin (Grade 3)	1	0	2	
Platelet count (Grade 3)	2	0	0	
Leukocytes (Grade 3)	1	0	0	
Lymphocytes (Grade 3)	2	2	3	
Lymphocytes (Grade 4)	1	0	0	
Aspartate Aminotransferase (Grade 3)	2	0	0	
Aspartate Aminotransferase (Grade 4)	1	0	0	
Alanine Aminotransferase (Grade 3)	1	1	0	
Alanine Aminotransferase (Grade 4)	1	0	0	

Bilirubin, TOTAL (Grade 4)	1	0	0	
Creatinine, (Grade 3)	0	1	0	
Potassium, (Grade 3)	1	1	0	
Amylase (Grade 3)	2	0	0	
Lipase (Grade 3)	4	0	1	
Albumin, (Grade 3)	1	0	0	
Hypokalemia (Grade 3)	1	1	0	
Platelet Count (Grade 4)	0	0	0	
Leukocytes (Grade 4)	0	0	0	
Absolute Neutrophil Count (Grade 3)	0	0	0	
Absolute Neutrophil Count (Grade 4)	0	0	0	
Alkaline Phosphatase (Grade 3)	0	0	0	
Alkaline Phosphatase (Grade 4)	0	0	0	
Bilirubin, Total (Grade 3)	0	0	0	
Creatinine (Grade 4)	0	0	0	
Sodium (Grade 3)	0	0	0	
Sodium (Grade 4)	0	0	0	
Potassium (Grade 4)	0	0	0	
Calcium (Grade 3)	0	0	0	
Calcium (Grade 4)	0	0	0	
Magnesium (Grade 3)	0	0	0	
Magnesium (Grade 4)	0	0	0	
Glucose (Grade 3)	0	0	0	
Glucose (Grade 4)	0	0	0	
Amylase (Grade 4)	0	0	0	
Lipase (Grade 4)	0	0	0	
Hypernatremia (Grade 3)	0	0	0	
Hypernatremia (Grade 4)	0	0	0	
Hyponatremia (Grade 3)	0	0	0	
Hyponatremia (Grade 4)	0	0	0	
Hyperkalemia (Grade 3)	0	0	0	
Hyperkalemia (Grade 4)	0	0	0	
Hypokalemia (Grade 4)	0	0	0	
Hypercalcemia (Grade 3)	0	0	0	
Hypercalcemia (Grade 4)	0	0	0	
Hypocalcemia (Grade 3)	0	0	0	
Hypocalcemia (Grade 4)	0	0	0	
Hypomagnesemia (Grade 3)	0	0	0	
Hypomagnesemia (Grade 4)	0	0	0	
Hypermagnesemia (Grade 3)	0	0	0	
Hypermagnesemia (Grade 4)	0	0	0	
Hypoglycemia (Grade 3)	0	0	0	
Hypoglycemia (Grade 4)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Laboratory Abnormalities in Specific Thyroid

Tests

End point title	Number of Participants with Laboratory Abnormalities in Specific Thyroid Tests[6]

End point description:

Blood samples were collected for specific thyroid test. All treated participants with at least one on-treatment thyroid stimulating hormone (TSH) measurement.

End point type	Primary

End point timeframe:

From first dose and 30 days after last dose of study therapy (up to approximately 25 months)

Notes:

[6] - 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: Statistical comparison was not required as per study design

End point values	NIVO+IPI+TACE	NIVO+TACE	TACE	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	9	8	
Units: participants				
TSH > ULN	5	5	5	
TSH > ULN with TSH <= ULN at baseline	5	4	3	
TSH > ULN with FT3/FT4 test value < LLN	3	1	3	
TSH > ULN with FT3/FT4 test values >= LLN	5	4	4	
TSH > ULN with FT3/FT4 test missing	0	2	1	
TSH < LLN	3	1	0	
TSH < LLN with TSH >= LLN at baseline	3	1	0	
TSH < LLN with FT3/FT4 test value > ULN	2	0	0	
With FT3/FT4 test values <= ULN	3	0	0	
With FT3/FT4 test missing	0	1	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Clinical Laboratory Abnormalities in Specific Liver Tests

End point title	Number of Participants with Clinical Laboratory Abnormalities in Specific Liver Tests[7]

End point description:

Blood samples were collected for specific liver tests. All treated participants.

End point type	Primary

End point timeframe:

From first dose and 30 days after last dose of study therapy (up to approximately 25 months)

Notes:

[7] - 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: Statistical comparison was not required as per study design

End point values	NIVO+IPI+TACE	NIVO+TACE	TACE	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	9	8	
Units: participants				
ALT or AST > 5 X ULN	3	2	0	
ALT or AST > 10 X ULN	2	1	0	
ALT or AST > 20 X ULN	1	0	0	
Total Bilirubin > 2 X ULN	3	2	1	
ALP > 1.5 X ULN	5	5	5	
ALT/AST > 3 X ULN total Bilirubin > 2 X ULN	3	1	0	
ALT/AST > 3XULN total Bilirubin>2XULN in 30 days	3	2	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality was collected from randomization until their study completion (up to approximately 38 months). SAEs and non-SAEs were collected from first dose to 100 days after last dose of study therapy (up to approximately 27 months).

Adverse event reporting additional description:

All treated participants included all enrolled participants who received at least one dose of any study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	NIVO + IPI + TACE

Reporting group description:

Participants with intermediate-stage hepatocellular carcinoma (HCC) received Nivolumab (NIVO) 240 milligram (mg) every 2 weeks (Q2W) and ipilimumab (IPI) 1 milligram per kilogram (mg/kg) every 6 weeks (Q6W) as an approximately 30-minute infusion. Participants received first Trans-arterial ChemoEmbolization (TACE) in in 7 days after randomization and then TACE as needed, until participant was no longer eligible for further TACE, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.

Reporting group title	NIVO + TACE

Reporting group description:

Participants with intermediate-stage hepatocellular carcinoma (HCC) received Nivolumab 240 milligram (mg) every 2 weeks (Q2W) as an approximately 30-minute infusion. Participants received first Trans-arterial ChemoEmbolization (TACE) in in 7 days after randomization and then TACE as needed, until participant was no longer eligible for further TACE, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.

Reporting group title	TACE

Reporting group description:

Participants received first Trans-arterial ChemoEmbolization (TACE) in in 7 days after randomization and then TACE as needed, until participant was no longer eligible for further TACE, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.

Serious adverse events	NIVO + IPI + TACE	NIVO + TACE	TACE
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 9 (77.78%)	6 / 9 (66.67%)	2 / 8 (25.00%)
number of deaths (all causes)	2	2	0
number of deaths resulting from adverse events	2	1	0
Investigations			
International normalised ratio increased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			

subjects affected / exposed	1 / 9 (11.11%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine aminotransferase increased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic encephalopathy			
subjects affected / exposed	2 / 9 (22.22%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 9 (11.11%)	3 / 9 (33.33%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	2 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			

subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (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
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (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
Diarrhoea			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (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
Haematemesis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (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
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	2 / 9 (22.22%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (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
Pleural effusion			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (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

Renal and urinary disorders			
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (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
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (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
Bursitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (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
Infections and infestations			
Klebsiella bacteraemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (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
Metabolism and nutrition disorders			
Cell death			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (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
Hyponatraemia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (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

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

Non-serious adverse events	NIVO + IPI + TACE	NIVO + TACE	TACE
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)	9 / 9 (100.00%)	8 / 8 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	2
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Raynaud's phenomenon			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Feeling hot			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Device related thrombosis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Asthenia			
subjects affected / exposed	2 / 9 (22.22%)	2 / 9 (22.22%)	1 / 8 (12.50%)
occurrences (all)	3	2	1
Pyrexia			
subjects affected / exposed	2 / 9 (22.22%)	3 / 9 (33.33%)	2 / 8 (25.00%)
occurrences (all)	2	5	3
Oedema peripheral			
subjects affected / exposed	1 / 9 (11.11%)	1 / 9 (11.11%)	3 / 8 (37.50%)
occurrences (all)	1	2	3
Mucosal inflammation			

subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Inflammation			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 9 (22.22%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	4	1	0
Dyspnoea			
subjects affected / exposed	1 / 9 (11.11%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Hiccups			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Pleural effusion			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Productive cough			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 9 (11.11%)	1 / 8 (12.50%)
occurrences (all)	1	1	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 9 (22.22%)	2 / 9 (22.22%)	1 / 8 (12.50%)
occurrences (all)	3	2	1
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 9 (22.22%)	2 / 9 (22.22%)	0 / 8 (0.00%)
occurrences (all)	3	6	0

Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Blood bilirubin increased			
subjects affected / exposed	0 / 9 (0.00%)	2 / 9 (22.22%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Blood creatinine increased			
subjects affected / exposed	2 / 9 (22.22%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	1 / 9 (11.11%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Gastric pH decreased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Weight increased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Weight decreased			
subjects affected / exposed	2 / 9 (22.22%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	2	4	0
Oxygen saturation decreased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Neutrophil count decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Lymphocyte count decreased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Lipase increased			

subjects affected / exposed	2 / 9 (22.22%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	4	0	0
Inflammatory marker increased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Hepatobiliary procedural complication			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Bone contusion			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Craniofacial fracture			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Fall			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Incision site pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Limb injury			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Post embolisation syndrome			
subjects affected / exposed	2 / 9 (22.22%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	2	0	2
Skin injury			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Tooth fracture			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Traumatic haematoma			

subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Cardiovascular disorder			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Tachycardia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 9 (11.11%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Encephalopathy			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Neuropathy peripheral			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Neuralgia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Hepatic encephalopathy			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	3	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 9 (0.00%)	2 / 9 (22.22%)	2 / 8 (25.00%)
occurrences (all)	0	4	2
Thrombocytopenia			

subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Neutropenia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Leukopenia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	3
Abdominal pain			
subjects affected / exposed	2 / 9 (22.22%)	3 / 9 (33.33%)	2 / 8 (25.00%)
occurrences (all)	3	6	5
Abdominal pain upper			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	2	0	1
Abdominal pain lower			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Anal haemorrhage			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Ascites			
subjects affected / exposed	1 / 9 (11.11%)	1 / 9 (11.11%)	1 / 8 (12.50%)
occurrences (all)	1	1	2
Chronic gastritis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Colitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Faeces discoloured			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1

Dental caries			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Dyspepsia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	2 / 8 (25.00%)
occurrences (all)	0	1	5
Diarrhoea			
subjects affected / exposed	3 / 9 (33.33%)	2 / 9 (22.22%)	3 / 8 (37.50%)
occurrences (all)	3	2	5
Constipation			
subjects affected / exposed	2 / 9 (22.22%)	2 / 9 (22.22%)	4 / 8 (50.00%)
occurrences (all)	3	2	4
Gastric ulcer			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	2
Gastritis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Varices oesophageal			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Stomatitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Portal hypertensive gastropathy			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	1 / 9 (11.11%)	2 / 9 (22.22%)	2 / 8 (25.00%)
occurrences (all)	3	3	5

Melaena			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Gastrointestinal angiodysplasia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Cholecystitis acute			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Psoriasis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Dermatitis contact			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Eczema			
subjects affected / exposed	2 / 9 (22.22%)	1 / 9 (11.11%)	1 / 8 (12.50%)
occurrences (all)	2	1	1
Erythema			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Onychoclasis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Photosensitivity reaction			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Pruritus			

subjects affected / exposed	3 / 9 (33.33%)	4 / 9 (44.44%)	2 / 8 (25.00%)
occurrences (all)	3	4	2
Skin hypopigmentation			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Rash maculo-papular			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Rash macular			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	2 / 9 (22.22%)	1 / 9 (11.11%)	3 / 8 (37.50%)
occurrences (all)	2	1	3
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Haematuria			
subjects affected / exposed	2 / 9 (22.22%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Hypertonic bladder			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Thyroiditis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Hypothyroidism			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Hyperthyroidism			

subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Adrenal insufficiency			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Psoriatic arthropathy			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Flank pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Bursitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Back pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	1 / 8 (12.50%)
occurrences (all)	0	2	1
Arthritis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Arthralgia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 9 (11.11%)	2 / 8 (25.00%)
occurrences (all)	1	2	2
Infections and infestations			
Bacteriuria			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Anal abscess			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Abdominal infection			

subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Cystitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
COVID-19			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Dermo-hypodermitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Genital herpes			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Enteritis infectious			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Pharyngitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Pneumonia			
subjects affected / exposed	2 / 9 (22.22%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	2	1	0
Respiratory tract infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	1 / 9 (11.11%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Urinary tract infection			
subjects affected / exposed	2 / 9 (22.22%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	3	0	0
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Influenza			

subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Herpes simplex			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Helicobacter infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Pneumonia aspiration			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Fluid retention			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Hypomagnesaemia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Decreased appetite			
subjects affected / exposed	1 / 9 (11.11%)	1 / 9 (11.11%)	3 / 8 (37.50%)
occurrences (all)	2	1	4
Hyperammonaemia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Hyperglycaemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Hyperkalaemia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Hypoalbuminaemia			
subjects affected / exposed	1 / 9 (11.11%)	2 / 9 (22.22%)	2 / 8 (25.00%)
occurrences (all)	2	7	3
Hypocalcaemia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	2

Hypoglycaemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Hypokalaemia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Diabetes mellitus			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Vitamin D deficiency			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 December 2021	Details of closure of the study with provision for participants currently on treatment or in the follow-up period to continue in the study as per the current protocol, study unblinding, Removal of placebo infusions for participants in Arms B and C, only safety assessment will be conducted, removal of on-study imaging assessments, align dose modification criteria and immuno-oncology agent management algorithms, Add the collection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection-related AEs and SAEs.

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.

Study was terminated due to slow accrual.

Notes: