



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 |
|-----------------|---|

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.

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|-----------------------|------|
| Reporting group title | TACE |
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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 |

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