Clinical trial results:
A Phase 2, Open-label, Multicenter Study to Investigate the Efficacy, Safety, and Pharmacokinetics of the Anti-PD-1 Monoclonal Antibody BGB-A317 in Patients with Previously Treated Hepatocellular Unresectable Carcinoma

Summary

EudraCT number	2017-003983-10
Trial protocol	GB DE ES PL IT
Global end of trial date	06 July 2022

Results information

Result version number	v1 (current)
This version publication date	19 July 2023
First version publication date	19 July 2023

Trial information

Trial identification

Sponsor protocol code	BGB-A317-208

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03419897
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 135200

Notes:

Sponsors

Sponsor organisation name	BeiGene, Ltd., c/o BeiGene USA, Inc.
Sponsor organisation address	1840 Gateway Drive, Third Floor, San Mateo, United States, 94404
Public contact	BeiGene Clinical Support, BeiGene Ltd., c/o BeiGene USA, Inc., 1- 877-828-5568, clinicaltrials@beigene.com
Scientific contact	BeiGene Clinical Support, BeiGene Ltd., c/o BeiGene USA, Inc., 1- 877-828-5568, clinicaltrials@beigene.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 January 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 July 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of BGB-A317 through Independent Review Committee (IRC) assessed objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 in previously treated, unresectable hepatocellular carcinoma (HCC)

Protection of trial subjects:

This trial was designed and monitored in accordance with Sponsor procedures, which comply with the ethical principles of GCP as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki. The IEC/IRB-approved ICF was signed and dated by the subject or the subject's legally authorized representative before his or her participation in the study. A copy of each signed ICF was provided to the subject or the subject's legally authorized representative. All signed and dated ICFs were retained in each patient's study file or in the site file. For any updated or revised ICFs, written informed consent was obtained using the IEC/IRB-approved updated/revised ICFs for continued participation in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 April 2018
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	Poland: 4
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	United Kingdom: 21
Country: Number of subjects enrolled	France: 77
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	China: 104
Country: Number of subjects enrolled	Taiwan: 18
Worldwide total number of subjects	249
EEA total number of subjects	106

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)	149
From 65 to 84 years	99
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 73 study centers in Mainland China, Taiwan, Italy, Germany, France, Spain, Poland, and the United Kingdom.

Pre-assignment

Screening details:

This study consisted of an initial screening phase (up to 28 days), a treatment phase, a safety follow-up phase, and a survival follow-up phase.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Tislelizumab

Arm description:

Tislelizumab 200 mg administered intravenously once every 3 weeks until unacceptable toxicity, withdrawal of consent, or the time point at which the subject was no longer benefiting from therapy, as assessed by the investigator, whichever occurred first

Arm type	Experimental
Investigational medicinal product name	Tislelizumab
Investigational medicinal product code	
Other name	A317
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Tislelizumab 200 mg administered intravenously once every 3 weeks

Number of subjects in period 1	Tislelizumab
Started	249
Completed	0
Not completed	249
Consent withdrawn by subject	6
Physician decision	1
Death	180
Lost to follow-up	1
Sponsor decision	61

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	249	249	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	60.3		
standard deviation	± 12.54	-	
Gender categorical Units: Subjects			
Female	32	32	
Male	217	217	
Eastern Cooperative Oncology Group Performance Status Score			
ECOG performance status is used by doctors and researchers to assess how a participant's disease is progressing, assess how the disease affects the daily living activities of the participant and determine appropriate treatment and prognosis. 0 = Fully Active (Most Favorable Activity); 1 = Restricted activity but ambulatory; 2 = Ambulatory but unable to carry out work activities; 3 = Limited Self-Care; 4 = Completely Disabled, No self-care (Least Favorable Activity)			
Units: Subjects			
Score 0	129	129	
Score 1	120	120	

End points

End points reporting groups

Reporting group title	Tislelizumab

Reporting group description:

Tislelizumab 200 mg administered intravenously once every 3 weeks until unacceptable toxicity, withdrawal of consent, or the time point at which the subject was no longer benefiting from therapy, as assessed by the investigator, whichever occurred first

Primary: Objective Response Rate (ORR) Assessed by Independent Review Committee (IRC)

End point title	Objective Response Rate (ORR) Assessed by Independent Review Committee (IRC)[1]

End point description:

ORR is defined as the percentage of subjects with complete response (CR) and partial response (PR) as the best overall response, as determined by an IRC using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. CR is defined as disappearance of all target lesions and PR is defined as at least a 30% decrease in the sum of diameters of target lesions.

End point type	Primary

End point timeframe:

From date of first dose to primary analysis data cut-off date of 30-June-2021 (up to approximately 3 years and 3
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: Single-arm study: superiority test, P=0.0001; P value was based on the exact binomial test comparing historical ORR rate of 7%

End point values	Tislelizumab			
Subject group type	Reporting group			
Number of subjects analysed	249			
Units: Percentage of subjects				
number (confidence interval 95%)	12.9 (8.96 to 17.66)			

Statistical analyses

No statistical analyses for this end point

Secondary: ORR Assessed by Investigator

End point title	ORR Assessed by Investigator

End point description:

ORR is defined as the percentage of subjects with CR and PR as the best overall response, as determined by investigator assessment using RECIST v1.1. CR is defined as disappearance of all target lesions and PR is defined as at least a 30% decrease in the sum of diameters of target lesions.

End point type	Secondary

End point timeframe:

From date of first dose to end of study (up to approximately 4 years and 3 months)

End point values	Tislelizumab			
Subject group type	Reporting group			
Number of subjects analysed	249			
Units: Percentage of subjects				
number (confidence interval 95%)	14.5 (10.34 to 19.45)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) Assessed by IRC

End point title	Duration of Response (DOR) Assessed by IRC

End point description:

DOR is defined as the time from the date that response criteria are first met to the date that progressive disease is objectively documented or death, whichever comes first, as assessed by the IRC using RECIST v1.1

End point type	Secondary

End point timeframe:

From date of first dose to end of study (up to approximately 4 years and 3 months)

End point values	Tislelizumab			
Subject group type	Reporting group			
Number of subjects analysed	249[2]			
Units: Months				
median (confidence interval 95%)	9999 (14.6 to 9999)			

Notes:

[2] - 9999 = median DOR not reached; confidence intervals not estimable due to insufficient events

Statistical analyses

No statistical analyses for this end point

Secondary: DOR Event-Free Rate Assessed by IRC

End point title	DOR Event-Free Rate Assessed by IRC

End point description:

DOR is defined as the time from the date that response criteria are first met to the date that progressive disease is objectively documented or death, whichever comes first, as assessed by the IRC using RECIST v1.1. The Kaplan-Meier method was used to estimate the percentage of subjects who were event-free for progression or death at 12 and 24 months with 95% confidence intervals estimated using Greenwood’s formula.

End point type	Secondary

End point timeframe:

From date of first dose to end of study (up to approximately 4 years and 3 months); Months 12 and 24 reported

End point values	Tislelizumab			
Subject group type	Reporting group			
Number of subjects analysed	249			
Units: Percentage of subjects				
number (confidence interval 95%)				
12 Months 24 Months	76.9 (57.5 to 88.3) 65.9 (45.7 to 80.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: DOR Assessed by Investigator

End point title	DOR Assessed by Investigator

End point description:

DOR is defined as the time from the date that response criteria are first met to the date that progressive disease is objectively documented or death, whichever comes first, as assessed by the investigator using RECIST v1.1

End point type	Secondary

End point timeframe:

From date of first dose to end of study (up to approximately 4 years and 3 months)

End point values	Tislelizumab			
Subject group type	Reporting group			
Number of subjects analysed	249[3]			
Units: Months				
median (confidence interval 95%)	21.4 (11.1 to 9999)			

Notes:

[3] - 9999 = Not estimable due to insufficient number of participants with events

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS) Assessed by IRC

End point title	Progression-free Survival (PFS) Assessed by IRC

End point description:

PFS is defined as the time from first dose until first documentation of progression or death, whichever comes first, as assessed by the IRC using RECIST v1.1

End point type	Secondary

End point timeframe:

From date of first dose to end of study (up to approximately 4 years and 3 months)

End point values	Tislelizumab			
Subject group type	Reporting group			
Number of subjects analysed	249			
Units: Months				
median (confidence interval 95%)	2.7 (1.4 to 2.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: PFS Assessed by Investigator

End point title	PFS Assessed by Investigator

End point description:

PFS is defined as the time from first dose until first documentation of progression or death, whichever comes first, as assessed by the investigator using RECIST v1.1

End point type	Secondary

End point timeframe:

From date of first dose to end of study (up to approximately 4 years and 3 months)

End point values	Tislelizumab			
Subject group type	Reporting group			
Number of subjects analysed	249			
Units: Months				
median (confidence interval 95%)	2.8 (2.6 to 4.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is defined as the time from first study drug administration to the date of death due to any cause

End point type	Secondary

End point timeframe:

From date of first dose to end of study (up to approximately 4 years and 3 months)

End point values	Tislelizumab			
Subject group type	Reporting group			
Number of subjects analysed	249			
Units: Months				
median (confidence interval 95%)	13.2 (10.8 to 15.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) Assessed by IRC

End point title	Disease Control Rate (DCR) Assessed by IRC

End point description:

DCR is defined as the percentage of subjects whose best overall response is CR, PR, or stable disease (SD) as assessed by the IRC using RECIST v1.1

End point type	Secondary

End point timeframe:

From date of first dose to end of study (up to approximately 4 years and 3 months)

End point values	Tislelizumab			
Subject group type	Reporting group			
Number of subjects analysed	249			
Units: Percentage of subjects				
number (confidence interval 95%)	53.0 (46.61 to 59.34)			

Statistical analyses

No statistical analyses for this end point

Secondary: DCR Assessed by Investigator

End point title	DCR Assessed by Investigator

End point description:

DCR is defined as the percentage of subjects whose best overall response is CR, PR, or stable disease (SD) as assessed by the investigator using RECIST v1.1

End point type	Secondary

End point timeframe:

From date of first dose to end of study (up to approximately 4 years and 3 months)

End point values	Tislelizumab			
Subject group type	Reporting group			
Number of subjects analysed	249			
Units: Percentage of subjects				
number (confidence interval 95%)	59.0 (52.65 to 65.20)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR) Assessed by IRC

End point title	Clinical Benefit Rate (CBR) Assessed by IRC

End point description:

CBR is defined as the percentage of subjects who have CR, PR, or SD of ≥ 24 weeks in duration as assessed by the IRC using RECIST v1.1

End point type	Secondary

End point timeframe:

From date of first dose to end of study (up to approximately 4 years and 3 months)

End point values	Tislelizumab			
Subject group type	Reporting group			
Number of subjects analysed	249			
Units: Percentage of subjects				
number (confidence interval 95%)	22.5 (17.46 to 28.19)			

Statistical analyses

No statistical analyses for this end point

Secondary: CBR Assessed by Investigator

End point title	CBR Assessed by Investigator

End point description:

CBR is defined as the percentage of subjects who have CR, PR, or SD of ≥ 24 weeks in duration as assessed by the investigator using RECIST v1.1

End point type	Secondary

End point timeframe:

Up to approximately 4 years and 3 months

End point values	Tislelizumab			
Subject group type	Reporting group			
Number of subjects analysed	249			
Units: Percentage of subjects				
number (confidence interval 95%)	30.9 (25.24 to 37.07)			

Statistical analyses

No statistical analyses for this end point

Secondary: European Quality of Life 5 Dimensions 5 Level Version (EQ-5D-5L) Visual Analogue Score (VAS)

End point title	European Quality of Life 5 Dimensions 5 Level Version (EQ-5D-5L) Visual Analogue Score (VAS)

End point description:

Mean change from baseline in EQ-5D-5L VAS. The EQ-5D-5L measures health outcomes using a VAS to record a subject's self-rated health on a scale from 0 to 100, where 100 is 'the best health you can imagine' and 0 is 'the worst health you can imagine.' A higher score indicates better health outcomes. n = number of subjects evaluable for this endpoint at various timepoints.

End point type	Secondary

End point timeframe:

Baseline to Cycle 6 Day 1 and Cycle 12 Day 1 (each cycle is 21 days)

End point values	Tislelizumab			
Subject group type	Reporting group			
Number of subjects analysed	202			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline; n = 202	75.2 (± 18.36)			
Change at Cycle 6; n = 107	2.4 (± 12.57)			
Change at Cycle 12; n = 49	4.7 (± 13.85)			

Statistical analyses

No statistical analyses for this end point

Secondary: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Global Health Status

End point title	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Global Health Status

End point description:

Mean change from baseline in EORTC QLQ-C30 Global Health Status/Quality of Life score. The EORTC QLQ-C30 v3.0 is a questionnaire that assesses quality of life of cancer patients. It includes global health status and quality of life questions related to overall health in which subjects respond based on a 7-point scale, where 1 is very poor and 7 is excellent. Raw scores are transformed into a 0 to 100 scale via linear transformation. A higher score indicates better health outcomes. n = number of subjects evaluable for this endpoint at various timepoints.

End point type	Secondary

End point timeframe:

Baseline to Cycle 6 Day 1 and Cycle 12 Day 1 (each cycle is 21 days)

End point values	Tislelizumab			
Subject group type	Reporting group			
Number of subjects analysed	238			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline; n = 238	71.8 (± 19.37)			
Change at Cycle 6; n = 127	-0.1 (± 17.50)			
Change at Cycle 12; n = 67	1.1 (± 18.63)			

Statistical analyses

No statistical analyses for this end point

Secondary: EORTC QLQ - Hepatocellular Carcinoma 18 Questions (HCC18): Index Scores

End point title	EORTC QLQ - Hepatocellular Carcinoma 18 Questions (HCC18): Index Scores

End point description:

Mean change from baseline in EORTC QLQ HCC18 Index Scores. The EORTC QLQ HCC18 is a specific questionnaire module that assesses quality of life of cancer patients related to overall health in which subjects respond based on a 7-point scale, where 1 is very poor and 7 is excellent. Raw scores are transformed into a 0 to 100 scale via linear transformation. A higher score indicates better health outcomes. n = number of subjects evaluable for this endpoint at various timepoints.

End point type	Secondary

End point timeframe:

Baseline to Cycle 6 Day 1 and Cycle 12 Day 1 (each cycle is 21 days)

End point values	Tislelizumab			
Subject group type	Reporting group			
Number of subjects analysed	236			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline; n = 236	13.6 (± 11.33)			
Change at Cycle 6; n = 129	1.4 (± 11.77)			
Change at Cycle 12; n = 60	0.1 (± 8.27)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Adverse Events

End point title	Number of Participants With Adverse Events

End point description:

Number of subjects with treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs), which includes laboratory tests, physical exams, electrocardiogram results and vital signs

End point type	Secondary

End point timeframe:

From first dose up to 30 days after the last dose of study drug; up to approximately 4 years and 3 months

End point values	Tislelizumab			
Subject group type	Reporting group			
Number of subjects analysed	249			
Units: Subjects				
number (not applicable)				
Subjects with at least 1 TEAE	236			
Subjects with a serious TEAE	94			

Statistical analyses

No statistical analyses for this end point

Secondary: DOR Event-Free Rate Assessed by Investigator

End point title	DOR Event-Free Rate Assessed by Investigator

End point description:

DOR is defined as the time from the date that response criteria are first met to the date that progressive disease is objectively documented or death, whichever comes first, as assessed by the investigator using RECIST v1.1. The Kaplan-Meier method was used to estimate the percentage of participants who were event-free for progression or death at 12 and 24 months with 95% confidence intervals estimated using Greenwood's formula.

End point type	Secondary

End point timeframe:

From date of first dose to end of study (up to approximately 4 years and 3 months); Months 12 and 24 reported

End point values	Tislelizumab			
Subject group type	Reporting group			
Number of subjects analysed	249			
Units: Percentage of subjects				
number (confidence interval 95%)				
12 Months	68.1 (49.8 to 80.9)			
24 Months	47.4 (30.1 to 62.8)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose to 30 days after last dose of study drug (up to approximately 4 years and 3 months)

Adverse event reporting additional description:

Defined as an adverse event that had an onset date or worsening in severity from baseline (pretreatment) on or after the date of first dose of study drug up to 30 days after study drug discontinuation or initiation of new anticancer therapy.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24

Reporting groups

Reporting group title	Tislelizumab

Reporting group description:

Tislelizumab 200 mg administered intravenously once every 3 weeks until unacceptable toxicity, withdrawal of consent, or the time point at which the participant no longer benefitted from therapy

Serious adverse events	Tislelizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	94 / 249 (37.75%)		
number of deaths (all causes)	180		
number of deaths resulting from adverse events	26		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	1 / 249 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour haemorrhage			
subjects affected / exposed	1 / 249 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Adenocarcinoma gastric			
subjects affected / exposed	1 / 249 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intracranial tumour haemorrhage			

subjects affected / exposed	1 / 249 (0.40%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Neoplasm swelling				
subjects affected / exposed	1 / 249 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Non-small cell lung cancer				
subjects affected / exposed	1 / 249 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal adenocarcinoma				
subjects affected / exposed	1 / 249 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Superior vena cava occlusion				
subjects affected / exposed	1 / 249 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chest pain				
subjects affected / exposed	2 / 249 (0.80%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	2 / 249 (0.80%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
General physical health deterioration				
subjects affected / exposed	3 / 249 (1.20%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 3			

Multiple organ dysfunction syndrome				
subjects affected / exposed	2 / 249 (0.80%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Pyrexia				
subjects affected / exposed	1 / 249 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Asthenia				
subjects affected / exposed	1 / 249 (0.40%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Dyspnoea				
subjects affected / exposed	1 / 249 (0.40%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	2 / 249 (0.80%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	2 / 249 (0.80%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Immune-mediated lung disease				
subjects affected / exposed	1 / 249 (0.40%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Haemothorax				
subjects affected / exposed	1 / 249 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			

Pulmonary haemorrhage			
subjects affected / exposed	1 / 249 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 249 (0.80%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 249 (2.01%)		
occurrences causally related to treatment / all	3 / 5		
deaths causally related to treatment / all	0 / 0		
Blood bilirubin increased			
subjects affected / exposed	3 / 249 (1.20%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Transaminases increased			
subjects affected / exposed	1 / 249 (0.40%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 249 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infusion related reaction			
subjects affected / exposed	1 / 249 (0.40%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure congestive			

subjects affected / exposed	1 / 249 (0.40%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Myocarditis				
subjects affected / exposed	2 / 249 (0.80%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Palpitations				
subjects affected / exposed	1 / 249 (0.40%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
VIth nerve paralysis				
subjects affected / exposed	1 / 249 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	1 / 249 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neuropathy peripheral				
subjects affected / exposed	1 / 249 (0.40%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Loss of consciousness				
subjects affected / exposed	1 / 249 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic encephalopathy				
subjects affected / exposed	2 / 249 (0.80%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Haemorrhage intracranial				

subjects affected / exposed	2 / 249 (0.80%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Brain oedema			
subjects affected / exposed	1 / 249 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Eyelid ptosis			
subjects affected / exposed	1 / 249 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	9 / 249 (3.61%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 2		
Abdominal pain upper			
subjects affected / exposed	2 / 249 (0.80%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	1 / 249 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	3 / 249 (1.20%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	1 / 249 (0.40%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Obstruction gastric			

subjects affected / exposed	1 / 249 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	1 / 249 (0.40%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Lower gastrointestinal haemorrhage				
subjects affected / exposed	1 / 249 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Immune-mediated enterocolitis				
subjects affected / exposed	1 / 249 (0.40%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Haemoperitoneum				
subjects affected / exposed	1 / 249 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haematemesis				
subjects affected / exposed	1 / 249 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric haemorrhage				
subjects affected / exposed	1 / 249 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Duodenal ulcer haemorrhage				
subjects affected / exposed	2 / 249 (0.80%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				

subjects affected / exposed	1 / 249 (0.40%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				
subjects affected / exposed	4 / 249 (1.61%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 3			
Varices oesophageal				
subjects affected / exposed	1 / 249 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 249 (0.40%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Jaundice cholestatic				
subjects affected / exposed	2 / 249 (0.80%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Acute hepatic failure				
subjects affected / exposed	1 / 249 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Bile duct stenosis				
subjects affected / exposed	1 / 249 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Budd-Chiari syndrome				
subjects affected / exposed	1 / 249 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic artery aneurysm				

subjects affected / exposed	1 / 249 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic failure				
subjects affected / exposed	7 / 249 (2.81%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 6			
Hepatic function abnormal				
subjects affected / exposed	4 / 249 (1.61%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Hepatitis				
subjects affected / exposed	1 / 249 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Hepatomegaly				
subjects affected / exposed	1 / 249 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatorenal syndrome				
subjects affected / exposed	1 / 249 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Hyperbilirubinaemia				
subjects affected / exposed	1 / 249 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Immune-mediated hepatitis				
subjects affected / exposed	2 / 249 (0.80%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Rash				

subjects affected / exposed	1 / 249 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hidradenitis			
subjects affected / exposed	1 / 249 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetic foot			
subjects affected / exposed	1 / 249 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 249 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	2 / 249 (0.80%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Primary adrenal insufficiency			
subjects affected / exposed	1 / 249 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 249 (0.80%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Myositis			
subjects affected / exposed	2 / 249 (0.80%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 249 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	2 / 249 (0.80%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	1 / 249 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peritonitis			
subjects affected / exposed	1 / 249 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pharyngitis			
subjects affected / exposed	1 / 249 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	5 / 249 (2.01%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 1		
Sepsis			
subjects affected / exposed	3 / 249 (1.20%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 249 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcal bacteraemia			

subjects affected / exposed	2 / 249 (0.80%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 249 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 249 (0.40%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	2 / 249 (0.80%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	1 / 249 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Tislelizumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	226 / 249 (90.76%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	14 / 249 (5.62%)		
occurrences (all)	16		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	32 / 249 (12.85%)		
occurrences (all)	43		
Oedema peripheral			

subjects affected / exposed	21 / 249 (8.43%)		
occurrences (all)	25		
Influenza like illness			
subjects affected / exposed	11 / 249 (4.42%)		
occurrences (all)	17		
Fatigue			
subjects affected / exposed	28 / 249 (11.24%)		
occurrences (all)	29		
Asthenia			
subjects affected / exposed	40 / 249 (16.06%)		
occurrences (all)	65		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	11 / 249 (4.42%)		
occurrences (all)	12		
Cough			
subjects affected / exposed	30 / 249 (12.05%)		
occurrences (all)	35		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	17 / 249 (6.83%)		
occurrences (all)	19		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	52 / 249 (20.88%)		
occurrences (all)	69		
Aspartate aminotransferase increased			
subjects affected / exposed	66 / 249 (26.51%)		
occurrences (all)	91		
Blood alkaline phosphatase increased			
subjects affected / exposed	21 / 249 (8.43%)		
occurrences (all)	28		
Blood bilirubin increased			
subjects affected / exposed	48 / 249 (19.28%)		
occurrences (all)	92		
Blood creatine phosphokinase MB			

increased			
subjects affected / exposed	14 / 249 (5.62%)		
occurrences (all)	16		
Blood creatine phosphokinase increased			
subjects affected / exposed	10 / 249 (4.02%)		
occurrences (all)	12		
Platelet count decreased			
subjects affected / exposed	21 / 249 (8.43%)		
occurrences (all)	43		
Neutrophil count decreased			
subjects affected / exposed	8 / 249 (3.21%)		
occurrences (all)	16		
Gamma-glutamyltransferase increased			
subjects affected / exposed	20 / 249 (8.03%)		
occurrences (all)	30		
Blood lactate dehydrogenase increased			
subjects affected / exposed	11 / 249 (4.42%)		
occurrences (all)	15		
Blood creatinine increased			
subjects affected / exposed	8 / 249 (3.21%)		
occurrences (all)	9		
Total bile acids increased			
subjects affected / exposed	8 / 249 (3.21%)		
occurrences (all)	13		
White blood cell count decreased			
subjects affected / exposed	17 / 249 (6.83%)		
occurrences (all)	36		
Weight decreased			
subjects affected / exposed	15 / 249 (6.02%)		
occurrences (all)	16		
Nervous system disorders			
Dizziness			
subjects affected / exposed	11 / 249 (4.42%)		
occurrences (all)	12		
Headache			

subjects affected / exposed	9 / 249 (3.61%)		
occurrences (all)	15		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	32 / 249 (12.85%)		
occurrences (all)	40		
Thrombocytopenia			
subjects affected / exposed	15 / 249 (6.02%)		
occurrences (all)	16		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	24 / 249 (9.64%)		
occurrences (all)	24		
Ascites			
subjects affected / exposed	19 / 249 (7.63%)		
occurrences (all)	19		
Abdominal pain upper			
subjects affected / exposed	17 / 249 (6.83%)		
occurrences (all)	18		
Abdominal pain			
subjects affected / exposed	26 / 249 (10.44%)		
occurrences (all)	31		
Abdominal distension			
subjects affected / exposed	21 / 249 (8.43%)		
occurrences (all)	22		
Vomiting			
subjects affected / exposed	21 / 249 (8.43%)		
occurrences (all)	21		
Stomatitis			
subjects affected / exposed	8 / 249 (3.21%)		
occurrences (all)	9		
Nausea			
subjects affected / exposed	15 / 249 (6.02%)		
occurrences (all)	18		
Diarrhoea			

subjects affected / exposed occurrences (all)	30 / 249 (12.05%) 44		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all)	 24 / 249 (9.64%) 29 35 / 249 (14.06%) 43		
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	 8 / 249 (3.21%) 11		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	 23 / 249 (9.24%) 27		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 25 / 249 (10.04%) 37 11 / 249 (4.42%) 15 12 / 249 (4.82%) 12 11 / 249 (4.42%) 14		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Pneumonia	 8 / 249 (3.21%) 9 		

subjects affected / exposed	9 / 249 (3.61%)		
occurrences (all)	11		
Upper respiratory tract infection			
subjects affected / exposed	11 / 249 (4.42%)		
occurrences (all)	12		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	43 / 249 (17.27%)		
occurrences (all)	49		
Hyperglycaemia			
subjects affected / exposed	15 / 249 (6.02%)		
occurrences (all)	34		
Hypoalbuminaemia			
subjects affected / exposed	18 / 249 (7.23%)		
occurrences (all)	24		
Hypokalaemia			
subjects affected / exposed	12 / 249 (4.82%)		
occurrences (all)	23		
Hyponatraemia			
subjects affected / exposed	8 / 249 (3.21%)		
occurrences (all)	8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 November 2017	• Modified inclusion criteria to include enrollment of subjects who have received emerging treatments such as lenvatinib or cabozantinib and address the issue regarding the lack of a 2nd line standard • Added an appendix to provide guidance regarding allowed 1st-line and 2nd-line treatment • Added the requirement that of the 228 subjects, at least 100 subjects will be enrolled who have had no more than 1 line of prior systemic therapy and at least 100 subjects will be enrolled who have had at least 2 lines of prior systemic therapy • Modified the frequency of radiological assessment of tumor response to ensure timely capture of response and progression in this subject population • Modified inclusion criteria to exclude the enrollment of subjects with an underlying medical condition or disease status unfavorable to the administration of study drug • Added eye exams and visual acuity testing for all subjects to monitor for potential ocular toxicities that have been associated with PD-1 inhibitors as a class • Added eye disorders and rheumatology to the table of recommended diagnostic tests for possible imTEAEs • Added management guidelines for diabetes/hyperglycemia, ocular toxicity, pancreatitis, arthritis, and mucositis/stomatitis to the treatment management table for imTEAEs
25 June 2018	• Updated the previously approximated number of participating study centers from “45” centers internationally to “80” to address increase in global site selection to meet enrollment target need • Revised sample size considerations • Revised inclusion criteria to indicate that subjects receiving antivirals at screening should have been treated for > 2 weeks prior to enrollment and should continue treatment • Updated contraception guidelines per the EU CTFG • Added assessment: Creatine kinase/creatine kinase-cardiac muscle isoenzyme (CK-MB) as additional assessment to monitor for myocarditis/myositis during the study • Added new appendix for BCLC staging classification to provide additional guidance to screening procedures

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/36872927

http://www.ncbi.nlm.nih.gov/pubmed/34518988