Clinical trial results:
A Randomized, Open-label, Multicenter Phase 3 Study to Compare the Efficacy and Safety of BGB-A317 Versus Sorafenib as First-Line Treatment in Patients With Unresectable Hepatocellular Carcinoma

Summary

EudraCT number	2017-002423-19
Trial protocol	GB DE CZ FR ES PL IT
Global end of trial date	14 December 2023

Results information

Result version number	v1 (current)
This version publication date	28 December 2024
First version publication date	28 December 2024

Trial information

Trial identification

Sponsor protocol code	BGB-A317-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03412773
WHO universal trial number (UTN)	-
Other trial identifiers	RATIONALE-301: BeiGene, JapicCTI-194569 : Japic, CTR20170882: ChinaDrugTrials

Notes:

Sponsors

Sponsor organisation name	BeiGene
Sponsor organisation address	1840 Gateway Drive, San Mateo, United States, 94404
Public contact	BeiGene Clinical Support, BeiGene, Inc., 1 877-828-5568, clinicaltrials@beigene.com
Scientific contact	BeiGene Clinical Support, BeiGene, 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	14 December 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 December 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This Phase 3 study was a global, multicenter trial that randomly assigned participants to either tislelizumab or sorafenib as a first-line treatment for adults with advanced liver cancer (hepatocellular carcinoma) that could not be surgically removed. Before enrolling Japanese participants in the main Phase 3 study, a preliminary assessment of safety and tolerability (the Safety Run-In Sub study) was conducted in Japan.

Protection of trial subjects:

This study was conducted in accordance with BeiGene procedures, which comply with the principles of Good Clinical Practice, International Council for Harmonization (ICH) of Technical Requirements for Pharmaceuticals for Human Use guidelines, the Declaration of Helsinki, and
local regulatory requirements.
The protocol, any amendments, and informed consent forms (ICFs) were reviewed and approved by the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) in conformance with Good Clinical Practice and applicable regulatory requirements.
The IEC/IRB-approved ICF was signed and dated by the patient or the patient’s legally
authorized representative before his or her participation in the study

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 December 2017
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	China: 411
Country: Number of subjects enrolled	Czechia: 3
Country: Number of subjects enrolled	Japan: 87
Country: Number of subjects enrolled	Taiwan: 14
Country: Number of subjects enrolled	United States: 19
Country: Number of subjects enrolled	Poland: 19
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	France: 50
Country: Number of subjects enrolled	Germany: 19
Country: Number of subjects enrolled	Italy: 37

Worldwide total number of subjects	684
EEA total number of subjects	143

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)	414
From 65 to 84 years	259
85 years and over	11

Subject disposition

Recruitment

Recruitment details:

The main study enrolled participants across Asia, Europe, and the U.S., with the first consented on December 18, 2017, and completion on December 14, 2023. A safety run-in sub-study in Japan assessed tislelizumab's safety in Japanese patients with hepatocellular carcinoma (HCC); these participants were not evaluated for the main study's endpoints.

Pre-assignment

Screening details:

The main study had four phases: Screening, Treatment, Safety Follow-up (up to 30 days post-treatment or 90 days post-tislelizumab for immune events), and Survival Follow-up (duration varied). Randomization was stratified by macrovascular invasion, extrahepatic spread, etiology, ECOG status (0 vs 1), and geography (Asia, Japan, Rest of World).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: Tislelizumab

Arm description:

Participants received 200 mg of intravenous tislelizumab every 3 weeks until intolerable toxicity, withdrawal of consent, or the investigator determined no further benefit from the therapy.

Arm type	Experimental
Investigational medicinal product name	Tislelizumab
Investigational medicinal product code	BGB-A317
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Tislelizumab 200 mg intravenously (IV) once every three weeks (Q3W)

Arm title	Arm B: Sorafenib

Arm description:

Participants received 400 mg of oral sorafenib twice daily until intolerable toxicity, consent withdrawal, or the investigator deemed no further benefit.

Arm type	Active comparator
Investigational medicinal product name	Sorafenib
Investigational medicinal product code	BAY43-9006
Other name	Nexavar
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sorafenib 400 mg orally (PO) twice daily (BID)

Arm title	Safety Run-In Sub-study

Arm description:

Japanese participants received 200 mg intravenous tislelizumab every 3 weeks to assess preliminary safety and tolerability.

Arm type	Safety Run-In Sub-study Arm
Investigational medicinal product name	Tislelizumab
Investigational medicinal product code	BGB-A317
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Tislelizumab 200 mg intravenously (IV) once every three weeks (Q3W)

Number of subjects in period 1	Arm A: Tislelizumab	Arm B: Sorafenib	Safety Run-In Sub-study
Started	342	332	10
Treated	338	324	10
Completed	0	0	0
Not completed	342	332	10
Consent withdrawn by subject	15	19	-
Physician decision	-	1	-
Death	259	273	7
Study Closed By Sponsor	46	33	3
Lost to follow-up	7	6	-
Transfer to LTE or Post Trial Supply	15	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Arm A: Tislelizumab
Reporting group description:	
Participants received 200 mg of intravenous tislelizumab every 3 weeks until intolerable toxicity, withdrawal of consent, or the investigator determined no further benefit from the therapy.	

Reporting group title	Arm B: Sorafenib
Reporting group description:	
Participants received 400 mg of oral sorafenib twice daily until intolerable toxicity, consent withdrawal, or the investigator deemed no further benefit.	

Reporting group title	Safety Run-In Sub-study
Reporting group description:	
Japanese participants received 200 mg intravenous tislelizumab every 3 weeks to assess preliminary safety and tolerability.	

Reporting group values	Arm A: Tislelizumab	Arm B: Sorafenib	Safety Run-In Sub-study
Number of subjects	342	332	10
Age categorical Units: Subjects			
18-64 years	206	207	1
65-84 years	129	121	9
>= 85 years	7	4	0
Age continuous Units: years			
arithmetic mean	60.45	59.51	71.70
standard deviation	± 12.528	± 12.737	± 8.247
Gender categorical Units: Subjects			
Female	53	51	3
Male	289	281	7
Eastern Cooperative Oncology Group (ECOG) Performance Status			
The ECOG scale assesses disease status from 0 to 5. A score of 0 means fully active with no restrictions, while 1 indicates limitations in strenuous activities but the ability to do light work. Score 2 signifies ambulatory and capable of self-care, yet unable to work, being active for over 50% of waking hours. Score 3 reflects limited self-care, confined to bed or a chair for more than half the day. Score 4 indicates complete disability, with the participant fully bedbound, and score 5 means deceased. Data are reported exclusively for participants in the main study.			
Units: Subjects			
Zero	182	180	9
One	160	152	1
Macrovascular Invasion			
Macrovascular invasion refers to the spread of cancer into large blood vessels near the tumor, and is associated with a more advanced stage of disease and a poorer prognosis. When present, cancer has infiltrated major blood vessels; when absent, no invasion into these vessels is detected, indicating a less aggressive disease.			
Units: Subjects			

Present	51	48	0
Absent	291	284	10
Extrahepatic Spread			
Extrahepatic spread refers to the spread of liver cancer beyond the liver to other organs or tissues. When present, cancer has metastasized outside the liver; when absent, the cancer is confined to the liver.			
Units: Subjects			
Present	219	198	4
Absent	123	134	6
Etiology			
Participants were grouped based on the presence of Hepatitis C virus or another virus, with those having both Hepatitis B and C classified under the "other" category.			
Units: Subjects			
Hepatitis C Virus	46	39	4
Other	296	293	6
Geographic Region Units: Subjects			
Asia Exluding Japan	215	210	0
Japan	38	39	10
European Union (EU)/United States (US)	89	83	0

Reporting group values	Total		
Number of subjects	684		
Age categorical Units: Subjects			
18-64 years	414		
65-84 years	259		
>= 85 years	11		
Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	107		
Male	577		
Eastern Cooperative Oncology Group (ECOG) Performance Status			
The ECOG scale assesses disease status from 0 to 5. A score of 0 means fully active with no restrictions, while 1 indicates limitations in strenuous activities but the ability to do light work. Score 2 signifies ambulatory and capable of self-care, yet unable to work, being active for over 50% of waking hours. Score 3 reflects limited self-care, confined to bed or a chair for more than half the day. Score 4 indicates complete disability, with the participant fully bedbound, and score 5 means deceased. Data are reported exclusively for participants in the main study.			
Units: Subjects			
Zero	371		
One	313		
Macrovascular Invasion			
Macrovascular invasion refers to the spread of cancer into large blood vessels near the tumor, and is associated with a more advanced stage of disease and a poorer prognosis. When present, cancer has infiltrated major blood vessels; when absent, no invasion into these vessels is detected, indicating a less aggressive disease.			

Units: Subjects			
Present	99		
Absent	585		
Extrahepatic Spread			
Extrahepatic spread refers to the spread of liver cancer beyond the liver to other organs or tissues. When present, cancer has metastasized outside the liver; when absent, the cancer is confined to the liver.			
Units: Subjects			
Present	421		
Absent	263		
Etiology			
Participants were grouped based on the presence of Hepatitis C virus or another virus, with those having both Hepatitis B and C classified under the "other" category.			
Units: Subjects			
Hepatitis C Virus	89		
Other	595		
Geographic Region Units: Subjects			
Asia Exluding Japan	425		
Japan	87		
European Union (EU)/United States (US)	172		

End points

End points reporting groups

Reporting group title	Arm A: Tislelizumab

Reporting group description:

Participants received 200 mg of intravenous tislelizumab every 3 weeks until intolerable toxicity, withdrawal of consent, or the investigator determined no further benefit from the therapy.

Reporting group title	Arm B: Sorafenib

Reporting group description:

Participants received 400 mg of oral sorafenib twice daily until intolerable toxicity, consent withdrawal, or the investigator deemed no further benefit.

Reporting group title	Safety Run-In Sub-study

Reporting group description:

Japanese participants received 200 mg intravenous tislelizumab every 3 weeks to assess preliminary safety and tolerability.

Primary: Safety Run-in Sub-study: Number of Participants With Adverse Events (AEs)

End point title	Safety Run-in Sub-study: Number of Participants With Adverse Events (AEs)[1][2]

End point description:

Number of participants with treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) was assessed per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03, using relevant physical examinations, electrocardiograms (ECGs), and laboratory assessments as needed.
An adverse event (AE) is any unfavorable or unintended sign (e.g., abnormal lab result), symptom, or disease temporally associated with study drug use, regardless of causality.
An SAE is defined as any adverse event that:
Results in death Is life-threatening Requires or prolongs hospitalization Causes disability/incapacity Leads to a congenital anomaly/birth defect Is deemed medically significant by the investigator (e.g., requiring intervention to prevent severe outcomes).

End point type	Primary

End point timeframe:

From the first dose to 30 days after the last dose, new anticancer therapy, or the analysis cutoff on 14 December 2023 (a maximum of 64 months)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This endpoint was not assessed in the safety run-in sub-study.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Safety data are reported as a secondary endpoint for participants in the main study.

End point values	Safety Run-In Sub-study			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Count of Participants				
TEAEs	8			
SAEs	1			

Statistical analyses

No statistical analyses for this end point

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)[3]

End point description:

Defined as the time from the date of randomization to the date of death due to any cause. Median OS was estimated using Kaplan-Meier methodology.

End point type	Primary

End point timeframe:

Through the primary analysis data cut-off date of July 11th, 2022 (up to approximately 55 months)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was not assessed in the safety run-in sub-study.

End point values	Arm A: Tislelizumab	Arm B: Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	342	332		
Units: Months				
median (confidence interval 95%)	15.9 (13.2 to 19.7)	14.1 (12.6 to 17.4)		

Statistical analyses

Statistical analysis title	Overall Survival (OS) Non-inferiority
Comparison groups	Arm A: Tislelizumab v Arm B: Sorafenib
Number of subjects included in analysis	674
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.712
upper limit	1.019

Notes:

[4] - Overall survival (OS) was compared between the tislelizumab group (Arm A) and the sorafenib group (Arm B) by testing the null hypothesis of noninferiority: the null hypothesis assumes the hazard ratio for tislelizumab versus sorafenib is greater than or equal to 1.08, while the alternative hypothesis assumes the hazard ratio is less than 1.08. Noninferiority was declared if the upper limit of the 95.003%

CI for the HR was less than 1.08.

Statistical analysis title	Overall Survival (OS) Superiority
Comparison groups	Arm A: Tislelizumab v Arm B: Sorafenib
Number of subjects included in analysis	674
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.0398 [6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.712
upper limit	1.019

Notes:

[5] - Superiority of tislelizumab over sorafenib was tested for OS using a stratified log-rank test in the ITT analysis set only when noninferiority was demonstrated. Superiority was declared if the one-sided pvalue
crosses the boundary of 0.0223 (1-sided p-value < 0.0223) in favor of Arm A in the stratified logrank test.

[6] - One-sided log-rank test stratified by geography (Asia vs EU/US), macrovascular invasion and/or extrahepatic spread (present vs. absent), etiology (HCV vs. Other) and ECOG (0 vs. 1).

Secondary: Overall Response Rate (ORR) as Assessed by Blinded Independent Review Committee (BIRC)

End point title	Overall Response Rate (ORR) as Assessed by Blinded Independent Review Committee (BIRC)[7]

End point description:

Defined as the percentage of participants who had partial response or complete response as determined by Blinded Independent Review Committee (BIRC) per the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 in all randomized participants with measurable disease at baseline.

End point type	Secondary

End point timeframe:

Through the primary analysis data cut-off date of July 11th, 2022 (up to approximately 55 months)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was not assessed in the safety run-in sub-study.

End point values	Arm A: Tislelizumab	Arm B: Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	342	332		
Units: Percentage of Participants				
number (confidence interval 95%)	14.3 (10.8 to 18.5)	5.4 (3.2 to 8.4)		

Statistical analyses

Statistical analysis title	ORR by BIRC

Statistical analysis description:

The null hypothesis assumed that ORR is equal in both groups, while the alternative hypothesis assumed ORR is higher in the tislelizumab group (Arm A).

Comparison groups	Arm A: Tislelizumab v Arm B: Sorafenib
Number of subjects included in analysis	674
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0003 [8]
Method	Cochran-Mantel-Haenszel

Notes:

[8] - The nominal P-value from the Cochran-Mantel-Haenszel chi-square test, conducted at a 0.05 significance level, was stratified by geography, macrovascular invasion/extrahepatic spread, etiology, and ECOG.

Secondary: Overall Response Rate (ORR) as Assessed by the Investigator

End point title	Overall Response Rate (ORR) as Assessed by the Investigator[9]

End point description:

Defined as the percentage of participants who had partial response or complete response as determined by investigator per RECIST v1.1 in all randomized participants with measurable disease at baseline.

End point type	Secondary

End point timeframe:

Through the study completion data cut-off date of December 14th, 2023 (up to approximately 65 months)

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was not assessed in the safety run-in sub-study.

End point values	Arm A: Tislelizumab	Arm B: Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	342	332		
Units: percentage of participants				
number (confidence interval 95%)	15.5 (11.8 to 19.8)	5.7 (3.5 to 8.8)		

Statistical analyses

Statistical analysis title	ORR by Investigator
Comparison groups	Arm A: Tislelizumab v Arm B: Sorafenib
Number of subjects included in analysis	674
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 [10]
Method	Cochran-Mantel-Haenszel

Notes:

[10] - The nominal P-value from the Cochran-Mantel-Haenszel chi-square test, conducted at a 0.05 significance level, was stratified by geography, macrovascular invasion/extrahepatic spread, etiology, and ECOG.

Secondary: Progression Free Survival (PFS) as Assessed by BIRC

End point title	Progression Free Survival (PFS) as Assessed by BIRC[11]

End point description:

Defined as the time from randomization to the first objectively documented disease progression, or death from any cause, whichever occurred first, as assessed by the BIRC per RECIST v1.1. Kaplan-Meier methodology was used to estimate the median PFS.

End point type	Secondary

End point timeframe:

Through the primary analysis data cut-off date of July 11th, 2022 (up to approximately 55 months)

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was not assessed in the safety run-in sub-study.

End point values	Arm A: Tislelizumab	Arm B: Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	342	332		
Units: Months				
median (confidence interval 95%)	2.1 (2.1 to 3.5)	3.4 (2.2 to 4.1)		

Statistical analyses

Statistical analysis title	PFS by BIRC
Comparison groups	Arm A: Tislelizumab v Arm B: Sorafenib
Number of subjects included in analysis	674
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.1364 [13]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	1.33

Notes:

[12] - The hazard ratio was derived from a Cox regression model with treatment as a covariate and stratified by geography (Asia vs. EU/US), macrovascular invasion/extrahepatic spread (present vs. absent), etiology (HCV vs. other), and ECOG score (0 vs. 1).

[13] - One sided Log-Rank Test stratified by geography (Asia vs EU/US), macrovascular invasion and/or extrahepatic spread (present vs. absent), etiology (HCV vs. Other) and ECOG (0 vs. 1).

Secondary: Progression Free Survival (PFS) as Assessed by the Investigator

End point title	Progression Free Survival (PFS) as Assessed by the Investigator[14]

End point description:

Defined as the time from randomization to the first objectively documented disease progression, or death from any cause, whichever occurred first, as assessed by the investigator per RECIST v1.1. Kaplan-Meier methodology was used to estimate the median PFS.

End point type	Secondary

End point timeframe:

Through the study completion data cut-off date of December 14th, 2023 (up to approximately 65 months)

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was not assessed in the safety run-in sub-study.

End point values	Arm A: Tislelizumab	Arm B: Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	342	332		
Units: Months				
median (confidence interval 95%)	2.1 (2.1 to 2.3)	4.0 (2.7 to 4.1)		

Statistical analyses

Statistical analysis title	PFS by Investigator

Statistical analysis description:

The hazard ratio was derived from a Cox regression model with treatment as a covariate and stratified by geography (Asia vs. EU/US), macrovascular invasion/extrahepatic spread (present vs. absent), etiology (HCV vs. other), and ECOG score (0 vs. 1).

Comparison groups	Arm A: Tislelizumab v Arm B: Sorafenib
Number of subjects included in analysis	674
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2622 [15]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.26

Notes:

[15] - One sided Log-Rank Test stratified by geography (Asia vs EU/US), macrovascular invasion and/or extrahepatic spread (present vs. absent), etiology (HCV vs. Other) and ECOG (0 vs. 1).

Secondary: Duration of Response (DOR) as Assessed by BIRC

End point title	Duration of Response (DOR) as Assessed by BIRC[16]

End point description:

Defined as the time from the first occurrence of a documented objective response until the first documentation of progression or death from any cause, whichever comes first, as determined by the BIRC per RECIST v1.1. Median DOR was estimated using Kaplan-Meier methodology.
ITT Analysis Set. Only participants with best overall response of complete response or partial response confirmed per RECIST v1.1 were included in the analysis, and percentages were based on the number of responders.

End point type	Secondary

End point timeframe:

Through the primary analysis data cut-off date of July 11th, 2022 (up to approximately 55 months)

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was not assessed in the safety run-in sub-study.

End point values	Arm A: Tislelizumab	Arm B: Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	18		
Units: Months				
median (confidence interval 95%)	36.1 (16.8 to 9999)	11.0 (6.2 to 14.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) as Assessed by the Investigator

End point title	Duration of Response (DOR) as Assessed by the Investigator[17]

End point description:

Defined as the time from the first occurrence of a documented objective response until the first documentation of progression or death from any cause, whichever comes first, as assessed by the investigator per RECIST v1.1. Median DOR was estimated using Kaplan-Meier methodology.

ITT Analysis Set. Only participants with best overall response of complete response or partial response confirmed per RECIST v1.1 were included in the analysis, and percentages were based on the number of responders.

End point type	Secondary

End point timeframe:

Through the study completion data cut-off date of December 14th, 2023 (up to approximately 65 months)

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was not assessed in the safety run-in sub-study.

End point values	Arm A: Tislelizumab	Arm B: Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	19		
Units: Months				
median (confidence interval 95%)	25.2 (18.1 to 46.8)	13.8 (6.2 to 20.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP) as Assessed by BIRC

End point title	Time to Progression (TTP) as Assessed by BIRC[18]

End point description:

Defined as the time from the date of randomization to the date of the first objectively documented tumor progression as assessed by the BIRC per RECIST v1.1.

End point type	Secondary

End point timeframe:

Through the primary analysis data cut-off date of July 11th, 2022 (up to approximately 55 months)

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was not assessed in the safety run-in sub-study.

End point values	Arm A: Tislelizumab	Arm B: Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	342	332		
Units: Months				
median (confidence interval 95%)	2.2 (2.1 to 3.6)	4.1 (2.2 to 4.1)		

Statistical analyses

Statistical analysis title	TPP by BIRC
Comparison groups	Arm A: Tislelizumab v Arm B: Sorafenib

Number of subjects included in analysis	674
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	= 0.0859 [20]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	1.38

Notes:

[19] - The hazard ratio was derived from a Cox regression model with treatment as a covariate and stratified by geography (Asia vs. EU/US), macrovascular invasion/extrahepatic spread (present vs. absent), etiology (HCV vs. other), and ECOG score (0 vs. 1).

[20] - One sided Log-Rank Test stratified by geography (Asia vs EU/US), macrovascular invasion and/or extrahepatic spread (present vs. absent), etiology (HCV vs. Other) and ECOG (0 vs. 1).

Secondary: Time to Progression (TTP) as Assessed by the Investigator

End point title	Time to Progression (TTP) as Assessed by the Investigator[21]

End point description:

Defined as the time from the date of randomization to the date of the first objectively documented tumor progression as assessed by the investigator per RECIST v1.1.

End point type	Secondary

End point timeframe:

Through the study completion data cut-off date of December 14th, 2023 (up to approximately 65 months)

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was not assessed in the safety run-in sub-study.

End point values	Arm A: Tislelizumab	Arm B: Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	342	332		
Units: Months				
median (confidence interval 95%)	2.1 (2.1 to 3.3)	4.1 (3.4 to 4.2)		

Statistical analyses

Statistical analysis title	TPP by Investigator
Comparison groups	Arm A: Tislelizumab v Arm B: Sorafenib

Number of subjects included in analysis	674
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1182 [22]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	1.34

Notes:

[22] - One sided Log-Rank Test stratified by geography (Asia vs EU/US), macrovascular invasion and/or extrahepatic spread (present vs. absent), etiology (HCV vs. Other) and ECOG (0 vs. 1).

Secondary: Disease Control Rate (DCR) as Assessed by the Investigator

End point title	Disease Control Rate (DCR) as Assessed by the Investigator[23]

End point description:

Defined as the percentage of participants whose best overall response (BOR) is complete response, partial response, or stable disease per RECIST v1.1.

End point type	Secondary

End point timeframe:

Through the study completion data cut-off date of December 14th, 2023 (up to approximately 65 months)

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was not assessed in the safety run-in sub-study.

End point values	Arm A: Tislelizumab	Arm B: Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	342	332		
Units: Percentage of Participants				
number (not applicable)	44.2	52.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR) as Assessed by BIRC

End point title	Clinical Benefit Rate (CBR) as Assessed by BIRC[24]

End point description:

Defined as the percentage of participants whose best overall response (BOR) is complete response, partial response, or stable disease greater than or equal to 24 weeks in duration, per RECIST v1.1.

End point type	Secondary

End point timeframe:

Through the primary analysis data cut-off date of July 11th, 2022 (up to approximately 55 months)

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was not assessed in the safety run-in sub-study.

End point values	Arm A: Tislelizumab	Arm B: Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	342	332		
Units: Percentage of Participants				
number (not applicable)	25.4	24.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR) as Assessed by the Investigator

End point title	Clinical Benefit Rate (CBR) as Assessed by the Investigator[25]

End point description:

Defined as the percentage of participants whose best overall response (BOR) is complete response, partial response, or stable disease greater than or equal to 24 weeks in duration, per RECIST v1.1.

End point type	Secondary

End point timeframe:

Through the study completion data cut-off date of December 14th, 2023 (up to approximately 65 months)

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was not assessed in the safety run-in sub-study.

End point values	Arm A: Tislelizumab	Arm B: Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	342	332		
Units: Percentage of Participants				
number (not applicable)	25.7	28.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Hepatocellular Carcinoma 18

Questions (EORTC QLQ HCC 18) Index Score

End point title	Change From Baseline in the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Hepatocellular Carcinoma 18 Questions (EORTC QLQ HCC 18) Index Score[26]

End point description:

The EORTC QLQ-HCC18 is a questionnaire specifically designed to assess health-related quality of life in participants with hepatocellular carcinoma. It includes six symptom scales measuring Fatigue (3 items), Jaundice (2 items), Body Image (2 items), Nutrition (5 items), Pain (2 items), Fever (2 items) and two single items measuring Sex Life and Abdominal Swelling. Participants respond on a scale from 1 = "Not at all" to 4 = "Very Much. Raw scores are transformed into a 0 to 100 scale using linear transformation. The HCC18 Index score is calculated from each of the 6 symptom scales and the 2 single items, and ranges from 0 to 100. Higher scores indicate greater symptom burden or worse quality of life.

End point type	Secondary

End point timeframe:

Baseline to Cycles 4 and 6 (Each cycle was 21 days)

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was not assessed in the safety run-in sub-study.

End point values	Arm A: Tislelizumab	Arm B: Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	342[27]	332[28]		
Units: Score on a Scale				
arithmetic mean (standard deviation)				
Cycle 4	0.5 (± 8.12)	3.2 (± 9.25)		
Cycle 6	1.2 (± 9.88)	3.6 (± 10.38)		

Notes:

[27] - 212 participants were analyzed in Cycle 4 and 160 participants in Cycle 6

[28] - 171 participants were analyzed in Cycle 4 and 134 participants in Cycle 6

Statistical analyses

No statistical analyses for this end point

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

End point title	Change From Baseline in the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Global Health Status/Quality of Life Score[29]

End point description:

The EORTC QLQ-C30 v3.0 is a questionnaire that assesses quality of life of participants with cancer. It includes global health status and quality of life questions related to overall health in which participants 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. Only participants with data at both baseline and corresponding post-baseline visit are included in the analysis at each time point.

End point type	Secondary

End point timeframe:

Baseline to Cycles 4 and 6 (Each cycle was 21 days)

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was not assessed in the safety run-in sub-study.

End point values	Arm A: Tislelizumab	Arm B: Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	342[30]	332[31]		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Cycle 4	0.5 (± 17.20)	-3.3 (± 19.25)		
Cycle 6	0.4 (± 17.99)	-3.4 (± 16.58)		

Notes:

[30] - 213 participants were analyzed in Cycle 4 and 161 participants in Cycle 6

[31] - 171 participants were analyzed in Cycle 4 and 133 participants in Cycle 6

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the European Quality of Life 5 Dimensions, 5-level (EQ5D-5L) Visual Analogue Scale (VAS)

End point title	Change From Baseline in the European Quality of Life 5 Dimensions, 5-level (EQ5D-5L) Visual Analogue Scale (VAS)[32]

End point description:

The EQ-5D-5L comprises a descriptive module and a Visual Analogue scale (VAS). The EQ VAS measures respondent's self-rated health status on a 0 to 100 scale, with 100 = 'the best health you can imagine' and 0 = 'the worst health you can imagine'. Higher scores on VAS indicate higher health status. Only participants with data at both baseline and corresponding post-baseline visit are included in the analysis at each time point.

End point type	Secondary

End point timeframe:

Baseline to Cycles 4 and 6 (Each cycle was 21 days)

Notes:

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was not assessed in the safety run-in sub-study.

End point values	Arm A: Tislelizumab	Arm B: Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	342[33]	332[34]		
Units: Score on a Scale				
arithmetic mean (standard deviation)				
Cycle 4	-0.4 (± 14.52)	-4.3 (± 12.92)		
Cycle 6	-0.2 (± 17.03)	-5.4 (± 13.09)		

Notes:

[33] - 213 participants were analyzed in Cycle 4 and 161 were analyzed in Cycle 6.

[34] - 170 participants were analyzed in Cycle 4 and 132 were analyzed in Cycle 6.

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[35]

End point description:

Number of participants with treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.

The Safety Analysis Set includes all patients randomized and received at least one dose of any study drug.

End point type	Secondary

End point timeframe:

From the first dose to 30 days after the last dose, new anticancer therapy, or the study completion analysis cutoff on December 14th, 2023 (a maximum of 61 months for participants in Arm A and 63 months for participants in Arm B).

Notes:

[35] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was assessed as a primary endpoint in the safety run-in sub-study.

End point values	Arm A: Tislelizumab	Arm B: Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	338	324		
Units: Participants				
TEAEs	325	324		
SAEs	104	91		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) as Assessed by BIRC

End point title	Disease Control Rate (DCR) as Assessed by BIRC[36]

End point description:

Defined as the percentage of participants whose best overall response (BOR) is complete response, partial response, or stable disease per RECIST v1.1.

End point type	Secondary

End point timeframe:

Through the primary analysis data cut-off date of July 11th, 2022 (up to approximately 55 months)

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was not assessed in the safety run-in sub-study.

End point values	Arm A: Tislelizumab	Arm B: Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	342	332		
Units: Percentage of Participants				
number (not applicable)	44.2	50.3		

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, new anticancer therapy, or the study completion analysis cutoff on December 14th, 2023 (a maximum of 61 months for participants in Arm A, 63 months in Arm B, and 64 months in the Safety Run-in sub-study).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Arm A: Tislelizumab

Reporting group description:

Participants received 200 mg of intravenous tislelizumab every 3 weeks until intolerable toxicity, withdrawal of consent, or the investigator determined no further benefit from the therapy.

Reporting group title	Arm B: Sorafenib

Reporting group description:

Participants received 400 mg of oral sorafenib twice daily until intolerable toxicity, consent withdrawal, or the investigator deemed no further benefit.

Reporting group title	Safety Run-In Sub-study

Reporting group description:

Japanese participants received 200 mg intravenous tislelizumab every 3 weeks to assess preliminary safety and tolerability.

Serious adverse events	Arm A: Tislelizumab	Arm B: Sorafenib	Safety Run-In Sub-study
Total subjects affected by serious adverse events			
subjects affected / exposed	104 / 338 (30.77%)	91 / 324 (28.09%)	1 / 10 (10.00%)
number of deaths (all causes)	258	273	7
number of deaths resulting from adverse events	16	17	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 338 (0.30%)	1 / 324 (0.31%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Intraductal papillary mucinous neoplasm			

subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Liver carcinoma ruptured			
subjects affected / exposed	2 / 338 (0.59%)	2 / 324 (0.62%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 2	1 / 1	0 / 0
Oesophageal adenocarcinoma			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Tumour pain			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Tumour rupture			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Cerebral infarction			
subjects affected / exposed	0 / 338 (0.00%)	3 / 324 (0.93%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipoma			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Vascular disorders			
Circulatory collapse			

subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Hypotension			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Peripheral vascular disorder			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Shock haemorrhagic			
subjects affected / exposed	0 / 338 (0.00%)	2 / 324 (0.62%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 2	0 / 0
Surgical and medical procedures			
Radiotherapy			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 338 (0.30%)	2 / 324 (0.62%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 0
Fatigue			
subjects affected / exposed	1 / 338 (0.30%)	2 / 324 (0.62%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gait disturbance			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
General physical health deterioration			
subjects affected / exposed	1 / 338 (0.30%)	4 / 324 (1.23%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 0
Malaise			
subjects affected / exposed	0 / 338 (0.00%)	2 / 324 (0.62%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 338 (0.30%)	3 / 324 (0.93%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 3	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	1 / 338 (0.30%)	1 / 324 (0.31%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 338 (0.00%)	2 / 324 (0.62%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	3 / 338 (0.89%)	5 / 324 (1.54%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	1 / 3	3 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Reproductive system and breast			

disorders			
Pelvic fluid collection			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 338 (0.00%)	4 / 324 (1.23%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 338 (0.30%)	2 / 324 (0.62%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatopulmonary syndrome			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Hydrothorax			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Immune-mediated lung disease			
subjects affected / exposed	2 / 338 (0.59%)	0 / 324 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Pulmonary alveolar haemorrhage			
subjects affected / exposed	0 / 338 (0.00%)	0 / 324 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pulmonary embolism			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Pulmonary mass			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Respiratory failure			
subjects affected / exposed	0 / 338 (0.00%)	2 / 324 (0.62%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 338 (1.48%)	4 / 324 (1.23%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	4 / 5	3 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	0 / 338 (0.00%)	2 / 324 (0.62%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 338 (0.59%)	0 / 324 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 338 (0.59%)	1 / 324 (0.31%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme abnormal			
subjects affected / exposed	2 / 338 (0.59%)	2 / 324 (0.62%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Transaminases increased			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Weight decreased			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Craniocerebral injury			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Extradural haematoma			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Fall			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Femur fracture			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Fracture			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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

Hepatic rupture			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Humerus fracture			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Limb injury			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Radiation oesophagitis			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 338 (1.78%)	5 / 324 (1.54%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	5 / 7	5 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 338 (0.00%)	2 / 324 (0.62%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Microvascular coronary artery disease			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Pericarditis			
subjects affected / exposed	1 / 338 (0.30%)	1 / 324 (0.31%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ventricular fibrillation			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Ventricular tachycardia			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Dizziness			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Encephalopathy			
subjects affected / exposed	1 / 338 (0.30%)	1 / 324 (0.31%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Hemiplegia			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Hepatic encephalopathy			
subjects affected / exposed	1 / 338 (0.30%)	2 / 324 (0.62%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoaesthesia			

subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Loss of consciousness			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Seizure			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Vocal cord paralysis			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Blood and lymphatic system disorders			
Cold type haemolytic anaemia			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Hypersplenism			
subjects affected / exposed	1 / 338 (0.30%)	1 / 324 (0.31%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphopenia			

subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Eye disorders			
Cataract			
subjects affected / exposed	2 / 338 (0.59%)	0 / 324 (0.00%)	0 / 10 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 338 (0.59%)	4 / 324 (1.23%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	2 / 338 (0.59%)	1 / 324 (0.31%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anorectal varices			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Ascites			
subjects affected / exposed	4 / 338 (1.18%)	4 / 324 (1.23%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 4	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic gastritis			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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

Colitis			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Duodenal ulcer			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Gastric haemorrhage			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 338 (0.59%)	2 / 324 (0.62%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoperitoneum			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Immune-mediated enterocolitis			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Intestinal obstruction			
subjects affected / exposed	3 / 338 (0.89%)	0 / 324 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intra-abdominal fluid collection			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Oesophageal varices haemorrhage			

subjects affected / exposed	3 / 338 (0.89%)	0 / 324 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	4 / 338 (1.18%)	1 / 324 (0.31%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Varices oesophageal			
subjects affected / exposed	2 / 338 (0.59%)	0 / 324 (0.00%)	0 / 10 (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
Vomiting			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Biliary obstruction			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Drug-induced liver injury			

subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Hepatic cirrhosis			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Hepatic failure			
subjects affected / exposed	4 / 338 (1.18%)	3 / 324 (0.93%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	3 / 4	2 / 3	0 / 0
deaths causally related to treatment / all	2 / 2	0 / 0	0 / 0
Hepatic function abnormal			
subjects affected / exposed	2 / 338 (0.59%)	1 / 324 (0.31%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic haemorrhage			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Hepatitis			
subjects affected / exposed	2 / 338 (0.59%)	1 / 324 (0.31%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	1 / 338 (0.30%)	2 / 324 (0.62%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated hepatitis			
subjects affected / exposed	3 / 338 (0.89%)	0 / 324 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			

subjects affected / exposed	3 / 338 (0.89%)	5 / 324 (1.54%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	1 / 3	1 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice cholestatic			
subjects affected / exposed	2 / 338 (0.59%)	0 / 324 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Jaundice hepatocellular			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Portal vein thrombosis			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Skin and subcutaneous tissue disorders			
Acute generalised exanthematous pustulosis			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Immune-mediated dermatitis			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Rash			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Rash maculo-papular			
subjects affected / exposed	0 / 338 (0.00%)	2 / 324 (0.62%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	3 / 338 (0.89%)	0 / 324 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Proteinuria			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 338 (0.59%)	1 / 324 (0.31%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Osteolysis			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Pain in extremity			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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

Psoriatic arthropathy			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Rhabdomyolysis			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Bacteraemia			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Biliary tract infection			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Bronchitis			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
COVID-19			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Colonic abscess			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Diverticulitis			

subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Gastroenteritis			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Infection			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Influenza			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Lung abscess			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Pneumonia			
subjects affected / exposed	5 / 338 (1.48%)	3 / 324 (0.93%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	1 / 5	0 / 3	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Pulmonary tuberculosis			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Pyelonephritis			

subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Sepsis			
subjects affected / exposed	1 / 338 (0.30%)	1 / 324 (0.31%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Tuberculosis			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Urosepsis			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (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
Varicella			
subjects affected / exposed	0 / 338 (0.00%)	0 / 324 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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
Hyperamylasaemia			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			

subjects affected / exposed	2 / 338 (0.59%)	0 / 324 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	3 / 338 (0.89%)	0 / 324 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophosphataemia			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	0 / 10 (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

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

Non-serious adverse events	Arm A: Tislelizumab	Arm B: Sorafenib	Safety Run-In Sub-study
Total subjects affected by non-serious adverse events			
subjects affected / exposed	313 / 338 (92.60%)	318 / 324 (98.15%)	8 / 10 (80.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	23 / 338 (6.80%)	90 / 324 (27.78%)	1 / 10 (10.00%)
occurrences (all)	27	126	1
Hypotension			
subjects affected / exposed	5 / 338 (1.48%)	2 / 324 (0.62%)	1 / 10 (10.00%)
occurrences (all)	5	2	3
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	34 / 338 (10.06%)	26 / 324 (8.02%)	0 / 10 (0.00%)
occurrences (all)	40	34	0
Fatigue			
subjects affected / exposed	36 / 338 (10.65%)	37 / 324 (11.42%)	3 / 10 (30.00%)
occurrences (all)	40	48	3
Infusion site extravasation			
subjects affected / exposed	0 / 338 (0.00%)	0 / 324 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Malaise			

subjects affected / exposed	13 / 338 (3.85%)	14 / 324 (4.32%)	0 / 10 (0.00%)
occurrences (all)	13	15	0
Oedema peripheral			
subjects affected / exposed	21 / 338 (6.21%)	16 / 324 (4.94%)	2 / 10 (20.00%)
occurrences (all)	25	16	2
Pyrexia			
subjects affected / exposed	56 / 338 (16.57%)	56 / 324 (17.28%)	4 / 10 (40.00%)
occurrences (all)	77	75	4
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	38 / 338 (11.24%)	25 / 324 (7.72%)	1 / 10 (10.00%)
occurrences (all)	44	27	1
Dysphonia			
subjects affected / exposed	1 / 338 (0.30%)	28 / 324 (8.64%)	0 / 10 (0.00%)
occurrences (all)	1	30	0
Dyspnoea			
subjects affected / exposed	12 / 338 (3.55%)	8 / 324 (2.47%)	0 / 10 (0.00%)
occurrences (all)	13	8	0
Epistaxis			
subjects affected / exposed	5 / 338 (1.48%)	8 / 324 (2.47%)	1 / 10 (10.00%)
occurrences (all)	5	10	1
Oropharyngeal pain			
subjects affected / exposed	5 / 338 (1.48%)	12 / 324 (3.70%)	1 / 10 (10.00%)
occurrences (all)	6	15	1
Pulmonary artery thrombosis			
subjects affected / exposed	0 / 338 (0.00%)	0 / 324 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	19 / 338 (5.62%)	17 / 324 (5.25%)	1 / 10 (10.00%)
occurrences (all)	20	21	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	93 / 338 (27.51%)	111 / 324 (34.26%)	0 / 10 (0.00%)
occurrences (all)	133	168	0
Amylase increased			

subjects affected / exposed	0 / 338 (0.00%)	4 / 324 (1.23%)	1 / 10 (10.00%)
occurrences (all)	0	5	1
Aspartate aminotransferase increased			
subjects affected / exposed	124 / 338 (36.69%)	135 / 324 (41.67%)	1 / 10 (10.00%)
occurrences (all)	179	213	1
Bilirubin conjugated increased			
subjects affected / exposed	28 / 338 (8.28%)	33 / 324 (10.19%)	0 / 10 (0.00%)
occurrences (all)	40	56	0
Blood alkaline phosphatase increased			
subjects affected / exposed	42 / 338 (12.43%)	37 / 324 (11.42%)	0 / 10 (0.00%)
occurrences (all)	69	52	0
Blood bilirubin increased			
subjects affected / exposed	74 / 338 (21.89%)	101 / 324 (31.17%)	1 / 10 (10.00%)
occurrences (all)	143	167	1
Blood bilirubin unconjugated increased			
subjects affected / exposed	12 / 338 (3.55%)	13 / 324 (4.01%)	0 / 10 (0.00%)
occurrences (all)	19	25	0
Blood creatine phosphokinase MB increased			
subjects affected / exposed	17 / 338 (5.03%)	13 / 324 (4.01%)	0 / 10 (0.00%)
occurrences (all)	20	17	0
Blood creatine phosphokinase increased			
subjects affected / exposed	20 / 338 (5.92%)	13 / 324 (4.01%)	0 / 10 (0.00%)
occurrences (all)	27	26	0
Blood creatinine increased			
subjects affected / exposed	9 / 338 (2.66%)	3 / 324 (0.93%)	1 / 10 (10.00%)
occurrences (all)	17	5	1
Blood lactate dehydrogenase increased			
subjects affected / exposed	24 / 338 (7.10%)	28 / 324 (8.64%)	0 / 10 (0.00%)
occurrences (all)	33	55	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	43 / 338 (12.72%)	42 / 324 (12.96%)	0 / 10 (0.00%)
occurrences (all)	61	51	0
Hepatitis C RNA increased			

subjects affected / exposed	0 / 338 (0.00%)	0 / 324 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Neutrophil count decreased			
subjects affected / exposed	30 / 338 (8.88%)	29 / 324 (8.95%)	1 / 10 (10.00%)
occurrences (all)	65	59	1
Platelet count decreased			
subjects affected / exposed	50 / 338 (14.79%)	69 / 324 (21.30%)	0 / 10 (0.00%)
occurrences (all)	81	106	0
Weight decreased			
subjects affected / exposed	35 / 338 (10.36%)	63 / 324 (19.44%)	0 / 10 (0.00%)
occurrences (all)	40	72	0
White blood cell count decreased			
subjects affected / exposed	32 / 338 (9.47%)	31 / 324 (9.57%)	0 / 10 (0.00%)
occurrences (all)	63	69	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 338 (0.00%)	2 / 324 (0.62%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
Post procedural fever			
subjects affected / exposed	0 / 338 (0.00%)	1 / 324 (0.31%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Procedural pain			
subjects affected / exposed	1 / 338 (0.30%)	1 / 324 (0.31%)	1 / 10 (10.00%)
occurrences (all)	1	1	1
Cardiac disorders			
Palpitations			
subjects affected / exposed	2 / 338 (0.59%)	4 / 324 (1.23%)	1 / 10 (10.00%)
occurrences (all)	2	4	2
Nervous system disorders			
Dizziness			
subjects affected / exposed	12 / 338 (3.55%)	8 / 324 (2.47%)	1 / 10 (10.00%)
occurrences (all)	16	10	1
Dysgeusia			
subjects affected / exposed	5 / 338 (1.48%)	2 / 324 (0.62%)	1 / 10 (10.00%)
occurrences (all)	6	2	1
Headache			

subjects affected / exposed	16 / 338 (4.73%)	17 / 324 (5.25%)	0 / 10 (0.00%)
occurrences (all)	19	20	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	41 / 338 (12.13%)	32 / 324 (9.88%)	3 / 10 (30.00%)
occurrences (all)	73	47	3
Leukopenia			
subjects affected / exposed	14 / 338 (4.14%)	18 / 324 (5.56%)	0 / 10 (0.00%)
occurrences (all)	29	26	0
Neutropenia			
subjects affected / exposed	3 / 338 (0.89%)	13 / 324 (4.01%)	0 / 10 (0.00%)
occurrences (all)	21	16	0
Thrombocytopenia			
subjects affected / exposed	15 / 338 (4.44%)	31 / 324 (9.57%)	0 / 10 (0.00%)
occurrences (all)	24	47	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	5 / 338 (1.48%)	1 / 324 (0.31%)	1 / 10 (10.00%)
occurrences (all)	5	1	2
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	32 / 338 (9.47%)	20 / 324 (6.17%)	1 / 10 (10.00%)
occurrences (all)	36	25	1
Abdominal pain			
subjects affected / exposed	38 / 338 (11.24%)	40 / 324 (12.35%)	0 / 10 (0.00%)
occurrences (all)	47	51	0
Abdominal pain upper			
subjects affected / exposed	18 / 338 (5.33%)	32 / 324 (9.88%)	1 / 10 (10.00%)
occurrences (all)	20	40	1
Ascites			
subjects affected / exposed	14 / 338 (4.14%)	8 / 324 (2.47%)	0 / 10 (0.00%)
occurrences (all)	14	8	0
Constipation			
subjects affected / exposed	28 / 338 (8.28%)	28 / 324 (8.64%)	0 / 10 (0.00%)
occurrences (all)	35	36	0
Diarrhoea			

subjects affected / exposed	38 / 338 (11.24%)	142 / 324 (43.83%)	1 / 10 (10.00%)
occurrences (all)	52	379	1
Dry mouth			
subjects affected / exposed	11 / 338 (3.25%)	10 / 324 (3.09%)	0 / 10 (0.00%)
occurrences (all)	13	11	0
Dyspepsia			
subjects affected / exposed	14 / 338 (4.14%)	10 / 324 (3.09%)	1 / 10 (10.00%)
occurrences (all)	15	18	2
Nausea			
subjects affected / exposed	27 / 338 (7.99%)	33 / 324 (10.19%)	0 / 10 (0.00%)
occurrences (all)	29	34	0
Stomatitis			
subjects affected / exposed	9 / 338 (2.66%)	17 / 324 (5.25%)	1 / 10 (10.00%)
occurrences (all)	10	23	2
Vomiting			
subjects affected / exposed	25 / 338 (7.40%)	16 / 324 (4.94%)	1 / 10 (10.00%)
occurrences (all)	31	25	1
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	13 / 338 (3.85%)	12 / 324 (3.70%)	0 / 10 (0.00%)
occurrences (all)	16	14	0
Hyperbilirubinaemia			
subjects affected / exposed	14 / 338 (4.14%)	16 / 324 (4.94%)	0 / 10 (0.00%)
occurrences (all)	25	30	0
Portal vein thrombosis			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	2 / 338 (0.59%)	75 / 324 (23.15%)	0 / 10 (0.00%)
occurrences (all)	2	76	0
Dermatitis			
subjects affected / exposed	5 / 338 (1.48%)	1 / 324 (0.31%)	1 / 10 (10.00%)
occurrences (all)	5	1	1
Dermatitis psoriasiform			

subjects affected / exposed	0 / 338 (0.00%)	0 / 324 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Dry skin			
subjects affected / exposed	12 / 338 (3.55%)	6 / 324 (1.85%)	1 / 10 (10.00%)
occurrences (all)	13	7	1
Erythema			
subjects affected / exposed	3 / 338 (0.89%)	11 / 324 (3.40%)	0 / 10 (0.00%)
occurrences (all)	3	11	0
Neurodermatitis			
subjects affected / exposed	1 / 338 (0.30%)	0 / 324 (0.00%)	1 / 10 (10.00%)
occurrences (all)	4	0	1
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 338 (0.30%)	203 / 324 (62.65%)	1 / 10 (10.00%)
occurrences (all)	1	231	1
Pruritus			
subjects affected / exposed	48 / 338 (14.20%)	25 / 324 (7.72%)	0 / 10 (0.00%)
occurrences (all)	58	28	0
Rash			
subjects affected / exposed	40 / 338 (11.83%)	56 / 324 (17.28%)	3 / 10 (30.00%)
occurrences (all)	50	65	4
Rash maculo-papular			
subjects affected / exposed	4 / 338 (1.18%)	15 / 324 (4.63%)	0 / 10 (0.00%)
occurrences (all)	4	17	0
Skin disorder			
subjects affected / exposed	0 / 338 (0.00%)	0 / 324 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Urticaria			
subjects affected / exposed	2 / 338 (0.59%)	1 / 324 (0.31%)	1 / 10 (10.00%)
occurrences (all)	2	2	1
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	11 / 338 (3.25%)	12 / 324 (3.70%)	0 / 10 (0.00%)
occurrences (all)	15	12	0
Renal impairment			

subjects affected / exposed	1 / 338 (0.30%)	1 / 324 (0.31%)	1 / 10 (10.00%)
occurrences (all)	1	1	1
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	15 / 338 (4.44%)	4 / 324 (1.23%)	0 / 10 (0.00%)
occurrences (all)	15	47	0
Hypothyroidism			
subjects affected / exposed	29 / 338 (8.58%)	12 / 324 (3.70%)	0 / 10 (0.00%)
occurrences (all)	33	12	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	40 / 338 (11.83%)	22 / 324 (6.79%)	0 / 10 (0.00%)
occurrences (all)	54	30	0
Back pain			
subjects affected / exposed	29 / 338 (8.58%)	20 / 324 (6.17%)	1 / 10 (10.00%)
occurrences (all)	32	24	1
Muscle spasms			
subjects affected / exposed	5 / 338 (1.48%)	12 / 324 (3.70%)	0 / 10 (0.00%)
occurrences (all)	6	16	0
Myalgia			
subjects affected / exposed	5 / 338 (1.48%)	11 / 324 (3.40%)	0 / 10 (0.00%)
occurrences (all)	5	17	0
Pain in extremity			
subjects affected / exposed	11 / 338 (3.25%)	12 / 324 (3.70%)	0 / 10 (0.00%)
occurrences (all)	11	18	0
Infections and infestations			
Folliculitis			
subjects affected / exposed	0 / 338 (0.00%)	2 / 324 (0.62%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
Gastroenteritis			
subjects affected / exposed	1 / 338 (0.30%)	1 / 324 (0.31%)	1 / 10 (10.00%)
occurrences (all)	1	1	1
Herpes zoster			
subjects affected / exposed	2 / 338 (0.59%)	1 / 324 (0.31%)	1 / 10 (10.00%)
occurrences (all)	2	1	1
Influenza			

subjects affected / exposed	5 / 338 (1.48%)	2 / 324 (0.62%)	1 / 10 (10.00%)
occurrences (all)	5	2	1
Nasopharyngitis			
subjects affected / exposed	11 / 338 (3.25%)	11 / 324 (3.40%)	2 / 10 (20.00%)
occurrences (all)	13	13	2
Oral candidiasis			
subjects affected / exposed	0 / 338 (0.00%)	4 / 324 (1.23%)	1 / 10 (10.00%)
occurrences (all)	0	4	1
Pyelonephritis			
subjects affected / exposed	0 / 338 (0.00%)	0 / 324 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	30 / 338 (8.88%)	13 / 324 (4.01%)	0 / 10 (0.00%)
occurrences (all)	40	15	0
Urinary tract infection			
subjects affected / exposed	12 / 338 (3.55%)	12 / 324 (3.70%)	1 / 10 (10.00%)
occurrences (all)	13	15	2
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	45 / 338 (13.31%)	57 / 324 (17.59%)	3 / 10 (30.00%)
occurrences (all)	53	60	3
Diabetes mellitus			
subjects affected / exposed	2 / 338 (0.59%)	0 / 324 (0.00%)	1 / 10 (10.00%)
occurrences (all)	2	0	1
Hyperglycaemia			
subjects affected / exposed	19 / 338 (5.62%)	18 / 324 (5.56%)	0 / 10 (0.00%)
occurrences (all)	54	24	0
Hypoalbuminaemia			
subjects affected / exposed	45 / 338 (13.31%)	32 / 324 (9.88%)	0 / 10 (0.00%)
occurrences (all)	81	44	0
Hypocalcaemia			
subjects affected / exposed	7 / 338 (2.07%)	15 / 324 (4.63%)	0 / 10 (0.00%)
occurrences (all)	9	22	0
Hypokalaemia			
subjects affected / exposed	21 / 338 (6.21%)	34 / 324 (10.49%)	1 / 10 (10.00%)
occurrences (all)	43	63	1

Hypomagnesaemia			
subjects affected / exposed	9 / 338 (2.66%)	12 / 324 (3.70%)	0 / 10 (0.00%)
occurrences (all)	24	18	0
Hyponatraemia			
subjects affected / exposed	20 / 338 (5.92%)	28 / 324 (8.64%)	0 / 10 (0.00%)
occurrences (all)	26	34	0
Hypophosphataemia			
subjects affected / exposed	9 / 338 (2.66%)	45 / 324 (13.89%)	0 / 10 (0.00%)
occurrences (all)	21	78	0
Hypoproteinaemia			
subjects affected / exposed	9 / 338 (2.66%)	10 / 324 (3.09%)	0 / 10 (0.00%)
occurrences (all)	12	12	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 September 2017	The primary purpose of this amendment was to incorporate feedback from regulatory authorities, align the protocol with the Sponsor's new protocol template, clarify items that were inconsistent in the original protocol, and add the new safety run-in substudy for the assessment of preliminary safety in Japanese patients with previously treated HCC. No patient was enrolled under Protocol Amendment 1.0. The major protocol changes and rationale for these changes were as follows: • Changed objectives/endpoint: to reflect the testing procedure described in the protocol and importance of efficacy endpoints, ORR was moved from primary to secondary objective, and DCR and CBR were moved from exploratory objective to secondary objective. • Added the safety run-in substudy to the study design to provide a preliminary safety assessment in Japanese patients prior to enrollment in randomized portion of the Phase 3 study (tislelizumab had not previously been administered in Japanese patients). • Modified inclusion criterion to reflect the PMDA's request to only enroll Japanese patients who have been previously treated in the safety run-in substudy. • Modified inclusion criterion to include only patients with Child Pugh A liver function for best assessment of effect in experimental arms. • Modified stratification factors at randomization to balance the two treatment arms: removed Child Pugh classification (Class A versus Class B); split extrahepatic spread (present versus absent) and macrovascular invasion (present versus absent) into 2 separate strata; added etiology and ECOG. • Modified inclusion criterion to include patients with moderate renal impairment (creatinine clearance ≥ 30 mL/min by estimated glomerular filtration rate). • Modified inclusion criterion to enroll patients with better liver synthetic function. • Modified inclusion criteria to avoid enrollment of any patients who may be concurrently pregnant.
03 October 2017	The primary purpose of this amendment was to incorporate feedback from the BGB-A317-301 steering committee that further refined study eligibility to (1) avoid barriers to enrollment and (2) exclude patients whose underlying medical condition or disease status would be unfavorable for the administration of study drug. It also clarified the safety management of immune-mediated adverse events (imAEs) and any inconsistencies between the main protocol and the Japan safety run-in substudy protocol. No patient was enrolled under Protocol Amendment 2.0. The major protocol changes and rationale for these changes were as follows: • Modified inclusion criterion and removed requirement for continuous HCV treatment to align as per recommendation from American Association for the Study of Liver Disease on the treatment and management of patients with HCV infection. • Modified exclusion criterion to exclude enrollment of patients whose underlying medical condition or disease status would have been unfavorable for the administration of study drug. • Modified exclusion criterion since extrahepatic spread of HCC to the central nervous system is very uncommon and assessment with MRI/CT scan ought to be conducted based on clinical signs/symptoms.

18 October 2017	The primary purpose of this amendment was to incorporate feedback from the FDA regarding safety monitoring for potential imAEs after administration of BGB-A317. The major protocol changes and rationale for these changes were as follows: • Removed the statement that follow-up of all drug-related SAEs and imAEs be stopped at initiation of subsequent anticancer therapy to be able to capture all possible delayed imAEs. The protocol was modified to ensure that the safety follow-up period was ≥ 90 days for all patients on the BGB-A317 arm, regardless of initiation of subsequent anticancer therapy. • Added eye exams and visual acuity testing conducted by a specialist at baseline and every 4 months for all patients, inclusive of optical coherence tomography or an appropriate similar diagnostic test to monitor for potential ocular toxicities that have been associated with PD-1 inhibitors as a class.
28 June 2018	The primary purpose of this amendment was to merge language from the country-specific Protocol Amendments 3.1 (Japan) and 3.4 (Germany), as well as to incorporate feedback from the FDA. The major protocol changes and rationale for these changes were as follows: • Incorporated changes from the Japan specific amendment 3.1 in the Japan substudy based on feedback from the Japan PMDA (details are provided below in the description of Protocol Amendment 3.1) • Incorporated changes from the Germany-specific Protocol Amendment 3.4 in the main study from the Paul-Ehrlich-Institut (details are provided below in the description of Protocol Amendment 3.4) • Incorporated measures to further decrease the potential risk for hepatitis viral reactivation based on feedback from the FDA • Added a new appendix which specified Chinese herbal medications that were not allowed during study treatment
11 May 2020	The primary purpose of this amendment was to revise the statistical assumptions (ie, HR, stopping boundaries) for the interim analysis of the primary endpoint (OS) based on available published data. Based on the revised assumptions, the timing for the interim analysis of OS was delayed from 75% (ie, 378 deaths) until approximately 80% (ie, 403 deaths) of the targeted number of OS events (approximately 504 deaths) had occurred. The planned futility analysis at interim was removed.

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/30969136

http://www.ncbi.nlm.nih.gov/pubmed/37796513

http://www.ncbi.nlm.nih.gov/pubmed/39435268