



Clinical trial results:

A Phase 2 Study of Pembrolizumab (MK-3475) as Monotherapy in Subjects With Advanced Hepatocellular Carcinoma (KEYNOTE-224)

Summary

EudraCT number	2015-004566-28
Trial protocol	DE SE GB BE FR IT
Global end of trial date	29 September 2023

Results information

Result version number	v1 (current)
This version publication date	04 September 2024
First version publication date	04 September 2024

Trial information

Trial identification

Sponsor protocol code	3475-224
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02702414
WHO universal trial number (UTN)	-
Other trial identifiers	MSD: KEYNOTE-224, JAPIC-CTI: 163434

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme LLC
Sponsor organisation address	126 East Lincoln Avenue, P.O. Box 2000, Rahway, NJ, United States, 07065
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.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	29 September 2023
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	29 September 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a efficacy and safety study of pembrolizumab (MK-3475, KEYTRUDA®) as monotherapy in participants with hepatocellular carcinoma (HCC) in two cohorts: participants with advanced HCC and with no curative option after disease progression on sorafenib or intolerance of sorafenib (Cohort 1) or who had not received treatment for systemic disease (Cohort 2). Study participants may receive pembrolizumab once every 3 weeks for up to 35 initial cycles (up to approximately 2 years) and a potential additional 17 cycles in a re-treatment phase (approximately an additional 1 year of treatment).

The primary objective of this study is to determine the Objective Response Rate (ORR) of pembrolizumab given as monotherapy in participants with HCC.

Effective with Amendment 7: Upon study completion, participants are discontinued and may be enrolled in a pembrolizumab extension study, if available.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 June 2016
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	Belgium: 39
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	France: 32
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Japan: 11
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	United States: 33
Worldwide total number of subjects	156
EEA total number of subjects	97

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)	52
From 65 to 84 years	99
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

This study had 2 cohorts with each cohort starting treatment at a different time period during the study.

One participant allocated to Cohort 1 withdrew from the study before receiving treatment. This participant was not eligible for safety or efficacy analysis.

Pre-assignment

Screening details:

Per protocol, final analyses of all outcome measures were planned to be performed during the first course of therapy and collection of adverse events and all-cause mortality were planned to be done in both first and second courses.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: HCC-Prior Systemic Therapy with Sorafenib

Arm description:

Participants with previously systemically treated Hepatocellular Carcinoma (HCC) received a pembrolizumab 200 mg intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 administrations. Participants who stopped pembrolizumab as a result of obtaining a confirmed complete response (CR) or those who stopped after receiving 35 trial treatments were eligible for an additional 17 trial treatments (approximately an additional 1 year of treatment) after progressive disease if they met the criteria for re-treatment.

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	MK-3475 KEYTRUDA®
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use , Intravenous use

Dosage and administration details:

IV Infusion

Arm title	Cohort 2: HCC-Systemic Therapy Naïve
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Arm description:

Participants with HCC who had not received treatment for systemic disease received a pembrolizumab 200 mg IV infusion on Day 1 of each 3-week cycle for up to 35 administrations. Participants who stopped pembrolizumab as a result of obtaining a confirmed complete response (CR) or those who stopped after receiving 35 trial treatments were eligible for an additional 17 trial treatments (approximately an additional 1 year of treatment) after progressive disease if they met the criteria for re-treatment.

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	MK-3475 KEYTRUDA®
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use , Intravenous use

Number of subjects in period 1	Cohort 1: HCC-Prior Systemic Therapy with Sorafenib	Cohort 2: HCC-Systemic Therapy Naïve
Started	105	51
Treated	104	51
Received Second Course of Pembrolizumab	4	1
Completed	0	0
Not completed	105	51
Consent withdrawn by subject	-	1
Death	96	42
Sponsor Decision	8	7
Lost to follow-up	-	1
Protocol deviation	1	-

Baseline characteristics

Reporting groups

Reporting group title	Cohort 1: HCC-Prior Systemic Therapy with Sorafenib
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Reporting group description:

Participants with previously systemically treated Hepatocellular Carcinoma (HCC) received a pembrolizumab 200 mg intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 administrations. Participants who stopped pembrolizumab as a result of obtaining a confirmed complete response (CR) or those who stopped after receiving 35 trial treatments were eligible for an additional 17 trial treatments (approximately an additional 1 year of treatment) after progressive disease if they met the criteria for re-treatment.

Reporting group title	Cohort 2: HCC-Systemic Therapy Naïve
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Reporting group description:

Participants with HCC who had not received treatment for systemic disease received a pembrolizumab 200 mg IV infusion on Day 1 of each 3-week cycle for up to 35 administrations. Participants who stopped pembrolizumab as a result of obtaining a confirmed complete response (CR) or those who stopped after receiving 35 trial treatments were eligible for an additional 17 trial treatments (approximately an additional 1 year of treatment) after progressive disease if they met the criteria for re-treatment.

Reporting group values	Cohort 1: HCC-Prior Systemic Therapy with Sorafenib	Cohort 2: HCC-Systemic Therapy Naïve	Total
Number of subjects	105	51	156
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	34	18	52
From 65-84 years	69	30	99
85 years and over	2	3	5
Age Continuous			
Units: Years			
arithmetic mean	67.4	67.7	-
standard deviation	± 8.2	± 10.3	-
Sex: Female, Male			
Units: Participants			
Female	19	7	26
Male	86	44	130
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	14	2	16
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	3	1	4
White	85	48	133
More than one race	1	0	1

Unknown or Not Reported	1	0	1
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	3	2	5
Not Hispanic or Latino	99	45	144
Unknown or Not Reported	3	4	7

End points

End points reporting groups

Reporting group title	Cohort 1: HCC-Prior Systemic Therapy with Sorafenib
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Reporting group description:

Participants with previously systemically treated Hepatocellular Carcinoma (HCC) received a pembrolizumab 200 mg intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 administrations. Participants who stopped pembrolizumab as a result of obtaining a confirmed complete response (CR) or those who stopped after receiving 35 trial treatments were eligible for an additional 17 trial treatments (approximately an additional 1 year of treatment) after progressive disease if they met the criteria for re-treatment.

Reporting group title	Cohort 2: HCC-Systemic Therapy Naïve
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Reporting group description:

Participants with HCC who had not received treatment for systemic disease received a pembrolizumab 200 mg IV infusion on Day 1 of each 3-week cycle for up to 35 administrations. Participants who stopped pembrolizumab as a result of obtaining a confirmed complete response (CR) or those who stopped after receiving 35 trial treatments were eligible for an additional 17 trial treatments (approximately an additional 1 year of treatment) after progressive disease if they met the criteria for re-treatment.

Subject analysis set title	Cohort 1: HCC-Prior Systemic Therapy with Sorafenib
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Subject analysis set type	Per protocol
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Subject analysis set description:

Participants with previously systemically treated HCC received a pembrolizumab 200 mg IV infusion on Day 1 of each 3-week cycle for up to 35 administrations. Participants who stopped pembrolizumab as a result of obtaining a confirmed complete response (CR) or those who stopped after receiving 35 trial treatments were eligible for an additional 17 trial treatments (approximately an additional 1 year of treatment) after progressive disease if they met the criteria for re-treatment.

Subject analysis set title	Cohort 1: HCC-Prior Systemic Therapy with Sorafenib
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Subject analysis set description:

Participants with previously systemically treated HCC received a pembrolizumab 200 mg IV infusion on Day 1 of each 3-week cycle for up to 35 administrations. Participants who stopped pembrolizumab as a result of obtaining a confirmed complete response (CR) or those who stopped after receiving 35 trial treatments were eligible for an additional 17 trial treatments (approximately an additional 1 year of treatment) after progressive disease if they met the criteria for re-treatment.

Subject analysis set title	Cohort 2: HCC-Systemic Therapy Naïve
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Subject analysis set type	Per protocol
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Subject analysis set description:

Participants with HCC who had not received treatment for systemic disease received a pembrolizumab 200 mg IV infusion on Day 1 of each 3-week cycle for up to 35 administrations. Participants who stopped pembrolizumab as a result of obtaining a confirmed complete response (CR) or those who stopped after receiving 35 trial treatments were eligible for an additional 17 trial treatments (approximately an additional 1 year of treatment) after progressive disease if they met the criteria for re-treatment.

Primary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR) ^{[1][2]}
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End point description:

ORR was defined as the percentage of participants who had a confirmed Complete Response (CR: Disappearance of all target and non-target lesions) or a Partial Response (PR: At least a 30% decrease in the sum of diameters of target and non-target lesions) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as assessed by blinded central imaging vendor. Participants with missing data were considered non-responders. The percentage of participants who experienced a CR or PR per RECIST 1.1 is presented. The analysis population included all participants who received at least one dose of study treatment during the first course of therapy.

End point type	Primary
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End point timeframe:

Up to approximately 34 months for Cohort 1 and up to approximately 28 months for Cohort 2

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: No between-arm analysis was conducted for this endpoint.

[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: No between-arm analysis was conducted for this endpoint.

End point values	Cohort 2: HCC-Systemic Therapy Naïve	Cohort 1: HCC-Prior Systemic Therapy with Sorafenib		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	51	104		
Units: Percentage of participants				
number (confidence interval 95%)	15.7 (7.0 to 28.6)	18.3 (11.4 to 27.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR) ^[3]
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End point description:

For participants who demonstrated a confirmed CR (disappearance of all target & non-target lesions) or PR (≥30% decrease in the sum of diameters [SD] of target & non-target lesions) per RECIST 1.1 as assessed by BICR; DOR was defined as time from first documented evidence of CR or PR until progressive disease (PD) or death. Participants who had not progressed, started new anti-cancer therapy, been lost to follow-up, or died at the time of analysis were censored at tumor assessment date. Per RECIST 1.1, PD was at least 20% increase in SD of target lesions & an absolute increase of at least 5 mm, OR unequivocal progression for non-target lesions, OR appearance of one or more new lesions. The DOR for all participants who had a confirmed CR or PR was presented. The analysis population included all participants who received at least 1 dose of study treatment & who had a confirmed CR or confirmed PR during the first course of therapy. A value of 9999 indicates that no data were calculated.

End point type	Secondary
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End point timeframe:

Up to approximately 34 months for Cohort 1 and up to approximately 28 months for Cohort 2

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: No between-arm analysis was conducted for this endpoint.

End point values	Cohort 2: HCC-Systemic Therapy Naïve	Cohort 1: HCC-Prior Systemic Therapy with Sorafenib		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	8	19		
Units: Months				
median (confidence interval 95%)	16.2 (3.1 to 9999)	21.0 (10.7 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR) ^[4]
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End point description:

DCR was defined as the percentage of participants who had a CR (disappearance of all target and non-target lesions), PR (at least a 30% decrease in the sum of diameters of target and non-target lesions), or Stable Disease (SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease [PD was at least 20% increase in SD of target lesions and an absolute increase of at least 5 mm, OR unequivocal progression for non-target lesions, OR appearance of one or more new lesions.]). CR, PR, and SD were evaluated per RECIST 1.1 as assessed by BICR. Participants with missing data were considered as participants whose disease was not under control. The percentage of participants who experienced a confirmed CR, PR, or SD was reported. The analysis population included all participants who received at least one dose of study treatment during the first course of therapy.

End point type	Secondary
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End point timeframe:

Up to approximately 34 months for Cohort 1 and up to approximately 28 months for Cohort 2

Notes:

[4] - 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: No between-arm analysis was conducted for this endpoint.

End point values	Cohort 2: HCC-Systemic Therapy Naïve	Cohort 1: HCC-Prior Systemic Therapy with Sorafenib		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	51	104		
Units: Percentage of participants				
number (confidence interval 95%)	56.9 (42.2 to 70.7)	61.5 (51.5 to 70.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP)

End point title	Time to Progression (TTP) ^[5]
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End point description:

TTP was defined as time from the first dose to the first documented disease progression per RECIST 1.1 as assessed by BICR. PD was at least a 20% increase in the SD of target lesions and an absolute increase of at least 5 mm, OR unequivocal progression for non-target lesions, OR appearance of one or more new lesions. If there was no documented disease progression, TTP was censored at last tumor assessment date. The TTP was analyzed using the product-limit (Kaplan-Meier) method for censored data. TTP per RECIST 1.1 was presented. The analysis population included all participants who received at least one dose of study treatment during the first course of therapy.

End point type	Secondary
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End point timeframe:

Up to approximately 34 months for Cohort 1 and up to approximately 28 months for Cohort 2

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: No between-arm analysis was conducted for this endpoint.

End point values	Cohort 2: HCC-Systemic Therapy Naïve	Cohort 1: HCC-Prior Systemic Therapy with Sorafenib		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	51	104		
Units: Months				
median (confidence interval 95%)	4.4 (2.5 to 8.6)	4.8 (3.9 to 7.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS) ^[6]
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End point description:

OS was determined for all participants and was defined as the time from the first dose to death due to any cause. Participants were censored at the last known alive date. The OS was analyzed using the product-limit (Kaplan-Meier) method for censored data. The OS is presented. The analysis population included all participants who received at least one dose of study treatment during the first course of therapy.

End point type	Secondary
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End point timeframe:

Up to approximately 34 months for Cohort 1 and up to approximately 28 months for Cohort 2

Notes:

[6] - 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: No between-arm analysis was conducted for this endpoint.

End point values	Cohort 2: HCC-Systemic Therapy Naïve	Cohort 1: HCC-Prior Systemic Therapy with Sorafenib		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	51	104		
Units: Months				
median (confidence interval 95%)	16.9 (8.3 to 23.1)	13.2 (9.7 to 15.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS) ^[7]
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End point description:

PFS was defined as the time from the first dose to the first documented PD or death due to any cause, whichever occurred first, per RECIST 1.1 as assessed by BICR. PD was at least a 20% increase in SD of target lesions and an absolute increase of at least 5 mm, OR unequivocal progression for non-target lesions, OR appearance of one or more new lesions. If there was no disease progression or death, participants were censored at the date of their last disease assessment. The PFS was analyzed using the

product-limit (Kaplan-Meier) method for censored data. PFS was presented. The analysis population included all participants who received at least one dose of study treatment during the first course of therapy.

End point type	Secondary
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End point timeframe:

Up to approximately 34 months for Cohort 1 and up to approximately 28 months for Cohort 2

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: No between-arm analysis was conducted for this endpoint.

End point values	Cohort 2: HCC-Systemic Therapy Naïve	Cohort 1: HCC-Prior Systemic Therapy with Sorafenib		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	51	104		
Units: Months				
median (confidence interval 95%)	4.3 (2.1 to 7.8)	4.9 (3.5 to 6.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experienced At Least One Adverse Event (AE)

End point title	Number of Participants Who Experienced At Least One Adverse Event (AE) ^[8]
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End point description:

An AE was defined as any untoward medical occurrence in a participant or clinical investigation participant administered a study treatment and which does not necessarily have to have a causal relationship with this treatment. An AE could be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a study treatment, whether or not considered related to the study treatment. Any worsening (i.e., any clinically significant adverse change infrequency and/or intensity) of a preexisting condition that was temporally associated with the use of study treatment, was also an AE. Per protocol, the number of participants who experienced at least one AE was presented for first course of therapy only. The analysis population included all participants who received at least one dose of study treatment during the first course of therapy.

End point type	Secondary
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End point timeframe:

Up to approximately 34 months for Cohort 1 and up to approximately 28 months for Cohort 2

Notes:

[8] - 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: No between-arm analysis was conducted for this endpoint.

End point values	Cohort 2: HCC-Systemic Therapy Naïve	Cohort 1: HCC-Prior Systemic Therapy with Sorafenib		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	51	104		
Units: Participants	49	101		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Discontinued Study Treatment Due to an Adverse Event (AE)

End point title	Number of Participants Who Discontinued Study Treatment Due to an Adverse Event (AE) ^[9]
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End point description:

An AE was defined as any untoward medical occurrence in a participant or clinical investigation participant administered a study treatment and which does not necessarily have to have a causal relationship with this treatment. An AE could be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a study treatment, whether or not considered related to the study treatment. Any worsening (i.e., any clinically significant adverse change infrequency and/or intensity) of a preexisting condition that was temporally associated with the use of study treatment, was also an AE. The number of participants who discontinued study treatment due to an AE was presented for first course of therapy only. The analysis population included all participants who received at least one dose of study treatment during the first course of therapy.

End point type	Secondary
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End point timeframe:

Up to approximately 34 months for Cohort 1 and up to approximately 28 months for Cohort 2

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: No between-arm analysis was conducted for this endpoint.

End point values	Cohort 2: HCC-Systemic Therapy Naïve	Cohort 1: HCC-Prior Systemic Therapy with Sorafenib		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	51	104		
Units: Participants	8	23		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 87 months

Adverse event reporting additional description:

All-cause mortality (ACM)=all allocated participants (n=156); AEs=all participants who received ≥ 1 dose of treatment. Disease progression was not considered an AE unless treatment related. Neoplasm progression (NP), malignant NP, and disease progression unrelated to treatment were excluded. The 1st and 2nd courses were reported separately.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	26.0
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Reporting groups

Reporting group title	Cohort1:HCC-Prior Systemic Therapy with Sorafenib-1st Course
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Reporting group description:

Participants with previously systemically treated HCC received a pembrolizumab 200 mg IV infusion on Day 1 of each 3-week cycle for up to 35 administrations. Participants who stopped pembrolizumab as a result of obtaining a confirmed complete response (CR) or those who stopped after receiving 35 trial treatments were eligible for an additional 17 trial treatments (approximately an additional 1 year of treatment) after progressive disease if they met the criteria for re-treatment.

Reporting group title	Cohort 2: HCC-Systemic Therapy Naïve-2nd Course
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Reporting group description:

Participants from Cohort 2 who met the criteria for re-treatment received a pembrolizumab 200 mg IV infusion on Day 1 of each 3-week cycle for up to 17 administrations.

Reporting group title	Cohort1:HCC-Prior Systemic Therapy with Sorafenib-2nd Course
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Reporting group description:

Participants from Cohort 1 who met the criteria for re-treatment received a pembrolizumab 200 mg IV infusion on Day 1 of each 3-week cycle for up to 17 administrations.

Reporting group title	Cohort 2: HCC-Systemic Therapy Naïve-1st Course
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Reporting group description:

Participants with HCC who had not received treatment for systemic disease received a pembrolizumab 200 mg IV infusion on Day 1 of each 3-week cycle for up to 35 administrations. Participants who stopped pembrolizumab as a result of obtaining a confirmed complete response (CR) or those who stopped after receiving 35 trial treatments were eligible for an additional 17 trial treatments (approximately an additional 1 year of treatment) after progressive disease if they met the criteria for re-treatment.

Serious adverse events	Cohort1:HCC-Prior Systemic Therapy with Sorafenib-1st Course	Cohort 2: HCC-Systemic Therapy Naïve-2nd Course	Cohort1:HCC-Prior Systemic Therapy with Sorafenib-2nd Course
Total subjects affected by serious adverse events			
subjects affected / exposed	44 / 104 (42.31%)	0 / 1 (0.00%)	0 / 4 (0.00%)
number of deaths (all causes)	94	0	2
number of deaths resulting from adverse events	11	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			

subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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 necrosis			
subjects affected / exposed	0 / 104 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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
Colon cancer			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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
Vascular disorders			
Hypovolaemic shock			
subjects affected / exposed	2 / 104 (1.92%)	0 / 1 (0.00%)	0 / 4 (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
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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
Chest pain			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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
Asthenia			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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
Pyrexia			
subjects affected / exposed	0 / 104 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulcer haemorrhage			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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
Fatigue			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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
Dyspnoea			
subjects affected / exposed	2 / 104 (1.92%)	0 / 1 (0.00%)	0 / 4 (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
Pulmonary embolism			
subjects affected / exposed	0 / 104 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 104 (1.92%)	0 / 1 (0.00%)	0 / 4 (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
Blood creatinine increased			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 104 (3.85%)	0 / 1 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	0 / 104 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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
Ventricular fibrillation			
subjects affected / exposed	0 / 104 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			

subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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
Cardiogenic shock			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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
Chronic left ventricular failure			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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
Myocarditis			
subjects affected / exposed	0 / 104 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block second degree			
subjects affected / exposed	0 / 104 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	0 / 104 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic encephalopathy			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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
Ischaemic stroke			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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
Presyncope			

subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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
Radiculopathy			
subjects affected / exposed	0 / 104 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 104 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 104 (2.88%)	0 / 1 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal vein occlusion			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 104 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	4 / 104 (3.85%)	0 / 1 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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

Gastritis haemorrhagic			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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 ulcer			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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
Constipation			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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
Colitis			
subjects affected / exposed	0 / 104 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune colitis			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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
Varices oesophageal			
subjects affected / exposed	0 / 104 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	3 / 104 (2.88%)	0 / 1 (0.00%)	0 / 4 (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
Umbilical hernia			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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	2 / 104 (1.92%)	0 / 1 (0.00%)	0 / 4 (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
Melaena			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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			
Hepatic cytolysis			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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 haemorrhage			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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
Immune-mediated hepatitis			
subjects affected / exposed	0 / 104 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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
Jaundice cholestatic			
subjects affected / exposed	2 / 104 (1.92%)	0 / 1 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			

Lichenoid keratosis			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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	0 / 104 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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
Renal failure			
subjects affected / exposed	2 / 104 (1.92%)	0 / 1 (0.00%)	0 / 4 (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
Endocrine disorders			
Hypophysitis			
subjects affected / exposed	0 / 104 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adrenal insufficiency			
subjects affected / exposed	2 / 104 (1.92%)	0 / 1 (0.00%)	0 / 4 (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
Musculoskeletal and connective tissue disorders			
Pathological fracture			
subjects affected / exposed	0 / 104 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myositis			

subjects affected / exposed	0 / 104 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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
Cellulitis			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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
Device related infection			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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
Gastroenteritis			
subjects affected / exposed	0 / 104 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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
Large intestine infection			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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
Pneumonia			
subjects affected / exposed	2 / 104 (1.92%)	0 / 1 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			

subjects affected / exposed	0 / 104 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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
Septic shock			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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
Pneumonia bacterial			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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
Sepsis			
subjects affected / exposed	3 / 104 (2.88%)	0 / 1 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	2 / 104 (1.92%)	0 / 1 (0.00%)	0 / 4 (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
Failure to thrive			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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
Diabetic ketoacidosis			

subjects affected / exposed	0 / 104 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 1 diabetes mellitus			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	0 / 4 (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

Serious adverse events	Cohort 2: HCC-Systemic Therapy Naïve-1st Course		
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 51 (41.18%)		
number of deaths (all causes)	42		
number of deaths resulting from adverse events	3		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tumour necrosis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colon cancer			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypovolaemic shock			

subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Asthenia			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ulcer haemorrhage			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fatigue			

subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood creatinine increased			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood bilirubin increased			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ventricular fibrillation			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac failure			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiogenic shock			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chronic left ventricular failure			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocarditis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Atrioventricular block second degree			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Nervous system disorders			
Encephalopathy			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatic encephalopathy			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ischaemic stroke			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Presyncope			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Radiculopathy			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Retinal vein occlusion			

subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroesophageal reflux disease			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastritis haemorrhagic			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Autoimmune colitis			

subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Varices oesophageal			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Umbilical hernia			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Melaena			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic cytolysis			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic failure			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic haemorrhage			

subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune-mediated hepatitis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Jaundice			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Jaundice cholestatic			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Lichenoid keratosis			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rash			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			

Hypophysitis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Adrenal insufficiency			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Pathological fracture			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myositis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cellulitis			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Gastroenteritis viral				
subjects affected / exposed	1 / 51 (1.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestine infection				
subjects affected / exposed	0 / 51 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	0 / 51 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Viral infection				
subjects affected / exposed	1 / 51 (1.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	0 / 51 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	0 / 51 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia bacterial				
subjects affected / exposed	0 / 51 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 51 (1.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				

Hyperkalaemia				
subjects affected / exposed	0 / 51 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Failure to thrive				
subjects affected / exposed	0 / 51 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diabetic metabolic decompensation				
subjects affected / exposed	0 / 51 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diabetic ketoacidosis				
subjects affected / exposed	1 / 51 (1.96%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Type 1 diabetes mellitus				
subjects affected / exposed	0 / 51 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	Cohort1:HCC-Prior Systemic Therapy with Sorafenib-1st Course	Cohort 2: HCC-Systemic Therapy Naïve-2nd Course	Cohort1:HCC-Prior Systemic Therapy with Sorafenib-2nd Course
Total subjects affected by non-serious adverse events			
subjects affected / exposed	96 / 104 (92.31%)	0 / 1 (0.00%)	4 / 4 (100.00%)
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	16 / 104 (15.38%)	0 / 1 (0.00%)	1 / 4 (25.00%)
occurrences (all)	19	0	1
Fatigue			
subjects affected / exposed	30 / 104 (28.85%)	0 / 1 (0.00%)	0 / 4 (0.00%)
occurrences (all)	40	0	0

Mucosal inflammation subjects affected / exposed occurrences (all)	2 / 104 (1.92%) 3	0 / 1 (0.00%) 0	0 / 4 (0.00%) 0
Pyrexia subjects affected / exposed occurrences (all)	5 / 104 (4.81%) 6	0 / 1 (0.00%) 0	0 / 4 (0.00%) 0
Oedema peripheral subjects affected / exposed occurrences (all)	20 / 104 (19.23%) 21	0 / 1 (0.00%) 0	1 / 4 (25.00%) 1
Respiratory, thoracic and mediastinal disorders			
Productive cough subjects affected / exposed occurrences (all)	6 / 104 (5.77%) 6	0 / 1 (0.00%) 0	0 / 4 (0.00%) 0
Pleural effusion subjects affected / exposed occurrences (all)	1 / 104 (0.96%) 1	0 / 1 (0.00%) 0	1 / 4 (25.00%) 1
Dyspnoea subjects affected / exposed occurrences (all)	11 / 104 (10.58%) 15	0 / 1 (0.00%) 0	1 / 4 (25.00%) 1
Cough subjects affected / exposed occurrences (all)	19 / 104 (18.27%) 21	0 / 1 (0.00%) 0	0 / 4 (0.00%) 0
Psychiatric disorders			
Insomnia subjects affected / exposed occurrences (all)	7 / 104 (6.73%) 7	0 / 1 (0.00%) 0	1 / 4 (25.00%) 1
Investigations			
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	23 / 104 (22.12%) 27	0 / 1 (0.00%) 0	0 / 4 (0.00%) 0
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	13 / 104 (12.50%) 16	0 / 1 (0.00%) 0	0 / 4 (0.00%) 0
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	6 / 104 (5.77%) 7	0 / 1 (0.00%) 0	1 / 4 (25.00%) 1

Weight decreased subjects affected / exposed occurrences (all)	6 / 104 (5.77%) 6	0 / 1 (0.00%) 0	0 / 4 (0.00%) 0
Serum ferritin decreased subjects affected / exposed occurrences (all)	0 / 104 (0.00%) 0	0 / 1 (0.00%) 0	1 / 4 (25.00%) 1
Blood bilirubin increased subjects affected / exposed occurrences (all)	9 / 104 (8.65%) 10	0 / 1 (0.00%) 0	0 / 4 (0.00%) 0
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	2 / 104 (1.92%) 2	0 / 1 (0.00%) 0	1 / 4 (25.00%) 1
Nervous system disorders Headache subjects affected / exposed occurrences (all)	7 / 104 (6.73%) 10	0 / 1 (0.00%) 0	0 / 4 (0.00%) 0
Dizziness subjects affected / exposed occurrences (all)	4 / 104 (3.85%) 4	0 / 1 (0.00%) 0	1 / 4 (25.00%) 1
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	11 / 104 (10.58%) 12	0 / 1 (0.00%) 0	2 / 4 (50.00%) 2
Gastrointestinal disorders Ascites subjects affected / exposed occurrences (all)	12 / 104 (11.54%) 12	0 / 1 (0.00%) 0	0 / 4 (0.00%) 0
Abdominal pain upper subjects affected / exposed occurrences (all)	10 / 104 (9.62%) 13	0 / 1 (0.00%) 0	0 / 4 (0.00%) 0
Abdominal pain subjects affected / exposed occurrences (all)	16 / 104 (15.38%) 18	0 / 1 (0.00%) 0	1 / 4 (25.00%) 1
Dyspepsia subjects affected / exposed occurrences (all)	3 / 104 (2.88%) 3	0 / 1 (0.00%) 0	0 / 4 (0.00%) 0

Nausea			
subjects affected / exposed	21 / 104 (20.19%)	0 / 1 (0.00%)	0 / 4 (0.00%)
occurrences (all)	21	0	0
Varices oesophageal			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Vomiting			
subjects affected / exposed	9 / 104 (8.65%)	0 / 1 (0.00%)	0 / 4 (0.00%)
occurrences (all)	15	0	0
Constipation			
subjects affected / exposed	18 / 104 (17.31%)	0 / 1 (0.00%)	1 / 4 (25.00%)
occurrences (all)	18	0	1
Dry mouth			
subjects affected / exposed	5 / 104 (4.81%)	0 / 1 (0.00%)	0 / 4 (0.00%)
occurrences (all)	5	0	0
Diarrhoea			
subjects affected / exposed	17 / 104 (16.35%)	0 / 1 (0.00%)	1 / 4 (25.00%)
occurrences (all)	21	0	3
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	14 / 104 (13.46%)	0 / 1 (0.00%)	0 / 4 (0.00%)
occurrences (all)	19	0	0
Dry skin			
subjects affected / exposed	2 / 104 (1.92%)	0 / 1 (0.00%)	1 / 4 (25.00%)
occurrences (all)	2	0	1
Night sweats			
subjects affected / exposed	6 / 104 (5.77%)	0 / 1 (0.00%)	0 / 4 (0.00%)
occurrences (all)	6	0	0
Pruritus			
subjects affected / exposed	24 / 104 (23.08%)	0 / 1 (0.00%)	1 / 4 (25.00%)
occurrences (all)	29	0	1
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Endocrine disorders			

Hypothyroidism subjects affected / exposed occurrences (all)	8 / 104 (7.69%) 9	0 / 1 (0.00%) 0	0 / 4 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Myalgia subjects affected / exposed occurrences (all)	8 / 104 (7.69%) 16	0 / 1 (0.00%) 0	2 / 4 (50.00%) 4
Muscle spasms subjects affected / exposed occurrences (all)	6 / 104 (5.77%) 8	0 / 1 (0.00%) 0	0 / 4 (0.00%) 0
Back pain subjects affected / exposed occurrences (all)	8 / 104 (7.69%) 8	0 / 1 (0.00%) 0	0 / 4 (0.00%) 0
Arthralgia subjects affected / exposed occurrences (all)	20 / 104 (19.23%) 31	0 / 1 (0.00%) 0	1 / 4 (25.00%) 1
Infections and infestations			
Urinary tract infection subjects affected / exposed occurrences (all)	3 / 104 (2.88%) 3	0 / 1 (0.00%) 0	0 / 4 (0.00%) 0
Rhinitis subjects affected / exposed occurrences (all)	1 / 104 (0.96%) 1	0 / 1 (0.00%) 0	0 / 4 (0.00%) 0
Pneumonia subjects affected / exposed occurrences (all)	3 / 104 (2.88%) 3	0 / 1 (0.00%) 0	1 / 4 (25.00%) 1
Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 104 (2.88%) 3	0 / 1 (0.00%) 0	0 / 4 (0.00%) 0
Bronchitis subjects affected / exposed occurrences (all)	4 / 104 (3.85%) 4	0 / 1 (0.00%) 0	1 / 4 (25.00%) 1
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	16 / 104 (15.38%) 18	0 / 1 (0.00%) 0	0 / 4 (0.00%) 0

Dehydration			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Vitamin D deficiency			
subjects affected / exposed	1 / 104 (0.96%)	0 / 1 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Hyperglycaemia			
subjects affected / exposed	3 / 104 (2.88%)	0 / 1 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Hypokalaemia			
subjects affected / exposed	2 / 104 (1.92%)	0 / 1 (0.00%)	1 / 4 (25.00%)
occurrences (all)	2	0	2
Hypophosphataemia			
subjects affected / exposed	4 / 104 (3.85%)	0 / 1 (0.00%)	1 / 4 (25.00%)
occurrences (all)	4	0	1

Non-serious adverse events	Cohort 2: HCC- Systemic Therapy Naïve-1st Course		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 51 (90.20%)		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	7 / 51 (13.73%)		
occurrences (all)	8		
Fatigue			
subjects affected / exposed	21 / 51 (41.18%)		
occurrences (all)	23		
Mucosal inflammation			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	4		
Pyrexia			
subjects affected / exposed	5 / 51 (9.80%)		
occurrences (all)	6		
Oedema peripheral			
subjects affected / exposed	14 / 51 (27.45%)		
occurrences (all)	15		
Respiratory, thoracic and mediastinal			

disorders			
Productive cough			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Pleural effusion			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	6 / 51 (11.76%)		
occurrences (all)	6		
Cough			
subjects affected / exposed	8 / 51 (15.69%)		
occurrences (all)	10		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 51 (7.84%)		
occurrences (all)	4		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Alanine aminotransferase increased			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Weight decreased			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Serum ferritin decreased			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Blood bilirubin increased			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		

Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	6 / 51 (11.76%)		
occurrences (all)	6		
Abdominal pain upper			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Abdominal pain			
subjects affected / exposed	8 / 51 (15.69%)		
occurrences (all)	9		
Dyspepsia			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Nausea			
subjects affected / exposed	4 / 51 (7.84%)		
occurrences (all)	6		
Varices oesophageal			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		

Constipation subjects affected / exposed occurrences (all)	4 / 51 (7.84%) 4		
Dry mouth subjects affected / exposed occurrences (all)	4 / 51 (7.84%) 4		
Diarrhoea subjects affected / exposed occurrences (all)	13 / 51 (25.49%) 15		
Skin and subcutaneous tissue disorders			
Rash subjects affected / exposed occurrences (all)	5 / 51 (9.80%) 5		
Dry skin subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 2		
Night sweats subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Pruritus subjects affected / exposed occurrences (all)	6 / 51 (11.76%) 8		
Renal and urinary disorders			
Pollakiuria subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Endocrine disorders			
Hypothyroidism subjects affected / exposed occurrences (all)	6 / 51 (11.76%) 6		
Musculoskeletal and connective tissue disorders			
Myalgia subjects affected / exposed occurrences (all)	5 / 51 (9.80%) 6		
Muscle spasms			

subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Back pain			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Arthralgia			
subjects affected / exposed	5 / 51 (9.80%)		
occurrences (all)	8		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	4		
Rhinitis			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Pneumonia			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	4 / 51 (7.84%)		
occurrences (all)	4		
Bronchitis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	8 / 51 (15.69%)		
occurrences (all)	9		
Dehydration			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Vitamin D deficiency			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Hyperglycaemia			

subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Hypokalaemia			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Hypophosphataemia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 April 2016	The major changes of amendment 1 (AM1) were addition to inclusion criteria of having a diagnosis of HCC by pathology report, central confirmation of measurable disease assessed per RECIST 1.1 for identifying target lesions, corrections to the cycle time points for tumor imaging and blood for biomarkers.
26 June 2017	The major change of AM2 was to add language to exclude subjects with a hypersensitivity to study drug.
23 February 2018	The major changes of AM4 were to add guidelines for management of immune-related adverse events, addition of flexibility to perform survival status follow-up, and to allow the Sponsor to collect information as needed to support ongoing analysis of the study survival data.
29 June 2018	The major change of AM6 were addition of a cohort for first-line treatment, increasing the trial duration and enrollment of participants in the trail, added Cohort 2 for participants with no prior systemic treatment for HCC.
12 April 2021	The major change of AM7 was to include the requirement of roll over of trial participants into an extension trial.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported