



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

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

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

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

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

| | |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

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

| | |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

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

| | |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

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]} |
|-----------------|---|

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

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] |
|-----------------|---|

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

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] |
|-----------------|---|

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

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] |
|-----------------|--|

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

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] |
|-----------------|--------------------------------------|

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

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] |
|-----------------|--|

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

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] |
|-----------------|---|

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

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] |
|-----------------|---|

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

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

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 26.0 |
|--------------------|------|

Reporting groups

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

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

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

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

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 |

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

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|---|-----------------|---------------|---------------|
| 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 | | |
| Gastrooesophageal 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