



Clinical trial results:

A Phase 1b/2 Study of Ibrutinib Combination Therapy in Selected Advanced Gastrointestinal And Genitourinary Tumors

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2015-003656-40 |
| Trial protocol | ES GB |
| Global end of trial date | 20 August 2021 |

Results information

| | |
|--------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 19 October 2022 |
| First version publication date | 10 February 2021 |
| Version creation reason | <ul style="list-style-type: none">New data added to full data setCompletion of additional cohorts |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | PCYC-1128-CA |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02599324 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Pharmacyclics LCC, an AbbVie Company |
| Sponsor organisation address | 1000 Gateway Blvd, South San Francisco, CA, United States, 94080 |
| Public contact | Clinical Trial information, Pharmacyclics LLC, Pharmacyclics LLC, an AbbVie Company, 1 4087740330, info@pcyc.com |
| Scientific contact | Clinical Trial information, Pharmacyclics LLC, Pharmacyclics LLC, an AbbVie Company, 1 4087740330, info@pcyc.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 | 20 August 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 20 August 2021 |
| Global end of trial reached? | Yes |
| Global end of trial date | 20 August 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Phase 1b:

Primary Objective:

- To determine the recommended Phase 2 dose (RP2D) of ibrutinib in combination with everolimus in renal cell carcinoma (RCC) in Cohort 1, paclitaxel in urothelial carcinoma (UC) in Cohort 2, docetaxel in gastric adenocarcinoma (GC) in Cohort 3, cetuximab in colorectal adenocarcinoma (CRC) in Cohort 4, and pembrolizumab in UC in Cohort 6.
- To confirm the RP2D of single agent ibrutinib in UC in Cohort 5.

Phase 2:

Primary Objectives:

- To assess progression-free survival (PFS) of ibrutinib in combination with everolimus in RCC (Cohort 1) and ibrutinib in combination with paclitaxel for UC (Cohort 2)
- To assess the overall response rate (ORR) of ibrutinib combination therapy in GC (Cohort 3), CRC (Cohort 4), UC (Cohort 6), and ibrutinib as a single agent in UC (Cohort 5).

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements.

Background therapy:

None

Evidence for comparator:

No comparators were used for this Phase 1b/2 cohort study. The combination partners were selected based on whether these were already approved for the different solid tumor indications.

| | |
|---|------------------|
| Actual start date of recruitment | 01 December 2015 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Korea, Republic of: 61 |
| Country: Number of subjects enrolled | Spain: 88 |
| Country: Number of subjects enrolled | United Kingdom: 33 |
| Country: Number of subjects enrolled | United States: 80 |
| Worldwide total number of subjects | 262 |
| EEA total number of subjects | 121 |

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) | 129 |
| From 65 to 84 years | 128 |
| 85 years and over | 5 |

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 38 sites in the US (18), South Korea (8), UK (4) and Spain (8). The first subject consented 01 Dec 2015 and the last visit of the last subjects for this analysis was 20 August 2021.

Pre-assignment

Screening details:

Disease-related cohort inclusion criteria included histologically confirmed RCC, GC or gastroesophageal junction adenocarcinoma, and K-RAS or N-RAS wild-type epidermal growth factor receptor-expressing CRC or advanced or metastatic urothelial carcinoma. Patients had to have 1 or more measurable lesions per RECIST 1.1 criteria.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

This was an open-label study; no blinding was performed. Subjects were enrolled into cohorts according to disease type.

Arms

| | |
|------------------------------|----------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Renal cell carcinoma |

Arm description:

Subjects were to receive ibrutinib PO qd in combination with everolimus (6 hours after ibrutinib) at a dose of 10 mg PO qd in 21-day cycles until unacceptable toxicity or disease progression occurred. If one component of the regimen was discontinued prior to RECIST 1.1 determined disease progression, the other component was to be continued until disease progression or unacceptable toxicity.

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | Ibrutinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Ibrutinib 840 mg, 560 mg, or 420 mg (6 x, 4 x, or 3 x 140 mg capsules, respectively) was administered PO qd with 8 ounces (approximately 240 mL) of water. The capsules were to be swallowed intact, and subjects were not to attempt to open capsules or dissolve them in water.

| | |
|--|------------|
| Investigational medicinal product name | Everolimus |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Everolimus 10 mg tablets were taken PO qd at the same time every day either consistently with food or consistently without food. Four x 2.5 mg tablets or 2 x 5.0 mg tablets could be substituted if 10 mg tablets were not available. Everolimus tablets were to be taken approximately 6 hours after ibrutinib capsules.

Everolimus was administered in continual 21-day cycles. The first dose was delivered in the clinic on Day 1, after which subsequent dosing was usually on an outpatient basis. Everolimus was to be dispensed to subjects on Day 1 of each cycle.

| | |
|------------------|------------------------|
| Arm title | Gastric Adenocarcinoma |
|------------------|------------------------|

Arm description:

Subjects were to receive ibrutinib administered PO qd in combination with docetaxel at a dose of 60 to 75 mg/sqm administered as a 60-minute IV infusion q3weeks in 21-day cycles until unacceptable toxicity or disease progression occurred. If one component of the regimen was discontinued prior to RECIST 1.1 determined disease progression, the other component was to be continued until disease progression or unacceptable toxicity.

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | Ibrutinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Ibrutinib 840 mg, 560 mg, or 420 mg (6 x, 4 x, or 3 x 140 mg capsules, respectively) was administered PO qd with 8 ounces (approximately 240 mL) of water. The capsules were to be swallowed intact, and subjects were not to attempt to open capsules or dissolve them in water.

| | |
|--|-----------------------|
| Investigational medicinal product name | Docetaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Docetaxel was administered as a 60-minute infusion (± 10 minutes) at a dose of 60 to 75 mg/sqm, given continually in 21-day cycles. Following the first dose of docetaxel combination therapy (on Cycle 1 Day 1), subjects were to remain in the clinic for 2 hours after completion of administration in order to assess any acute toxicity. On days when ibrutinib was to be administered, ibrutinib was to be taken in the clinic approximately 30 minutes prior to commencement of IV drug delivery. If an episode of febrile neutropenia, prolonged neutropenia, or neutropenic infection occurred despite use of granulocyte-colony stimulating factor, the docetaxel dose was to be reduced from 75 to 60 mg/sqm.

| | |
|------------------|---------------------------|
| Arm title | Colorectal Adenocarcinoma |
|------------------|---------------------------|

Arm description:

Subjects were to receive ibrutinib administered PO qd in combination with cetuximab at a dose of 400 mg/sqm administered initially as a 120-minute IV infusion, then weekly 250 mg/sqm IV over 60 minutes in 21-day cycles until unacceptable toxicity or disease progression occurred. If one component of the regimen was discontinued prior to RECIST 1.1 determined disease progression, the other component was to be continued until disease progression or unacceptable toxicity.

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | Ibrutinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Ibrutinib 840 mg, 560 mg, or 420 mg (6 x, 4 x, or 3 x 140 mg capsules, respectively) was administered PO qd with 8 ounces (approximately 240 mL) of water. The capsules were to be swallowed intact, and subjects were not to attempt to open capsules or dissolve them in water.

| | |
|--|-----------------------|
| Investigational medicinal product name | Cetuximab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

The recommended initial dose of cetuximab was 400 mg/sqm administered as a 120-minute IV infusion. The recommended subsequent weekly dose (all other infusions) was 250 mg/sqm infused over 60 minutes. On days when ibrutinib was to be administered, ibrutinib was to be taken in the clinic approximately 30 minutes prior to commencement of IV drug delivery.

| | |
|------------------|---------------------------------|
| Arm title | Urothelial carcinoma paclitaxel |
|------------------|---------------------------------|

Arm description:

In Phase 1b, patients in Cohort 2 (UC) were treated first with Ibrutinib 560 mg PO qd and Paclitaxel 80 mg/m² IV, once weekly in continual 3 weekly cycles (4 patients) followed by Ibrutinib 840 mg and the same dose of Paclitaxel (10 patients). In Phase 2, 49 additional patients were treated with Ibrutinib 840 mg PO qd and Paclitaxel 80 mg/m² IV. Treatment was given until disease progression or unacceptable toxicity. If one component of the regimen was discontinued prior to RECIST 1.1 determined disease progression, the other component was to be continued until disease progression or unacceptable toxicity.

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | ibrutinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

In Phase 1b, patients in Cohort 2 (UC) were treated first with Ibrutinib 560 mg PO qd and Paclitaxel 80 mg/m² IV (4 patients) followed by Ibrutinib 840 mg and the same dose of Paclitaxel (10 patients). In Phase 2, 57 additional patients were treated with Ibrutinib 840 mg PO qd and Paclitaxel 80 mg/m² IV

| | |
|--|---|
| Investigational medicinal product name | paclitaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

In Phase 1b, patients in Cohort 2 (UC) were treated first with Ibrutinib 560 mg PO qd and Paclitaxel 80 mg/m² IV (4 patients) followed by Ibrutinib 840 mg and the same dose of Paclitaxel (10 patients). In Phase 2, 57 additional patients were treated with Ibrutinib 840 mg PO qd and Paclitaxel 80 mg/m² IV

| | |
|------------------|-------------------------------------|
| Arm title | Urothelial carcinoma ibrutinib mono |
|------------------|-------------------------------------|

Arm description:

Monotherapy with ibrutinib 840 mg daily until treatment progression or unacceptable toxicity.

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | ibrutinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

ibrutinib 840 mg po daily

| | |
|------------------|------------------------------------|
| Arm title | Urothelial carcinoma pembrolizumab |
|------------------|------------------------------------|

Arm description:

Patients were treated with Ibrutinib 560 mg PO qd and pembrolizumab 200 mg as 30 min intravenous infusion, once weekly in continual 3 weekly cycles. Treatment was given until disease progression or unacceptable toxicity. If one component of the regimen was discontinued prior to RECIST 1.1 determined disease progression, the other component was to be continued until disease progression or unacceptable toxicity.

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | ibrutinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

ibrutinib 560 mg once daily.

| | |
|--|---|
| Investigational medicinal product name | pembrolizumumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

pembrolizumumab 200 mg as intravenous infusion for 30 minutes weekly in 3-weekly cycles

| Number of subjects in period 1 | Renal cell carcinoma | Gastric Adenocarcinoma | Colorectal Adenocarcinoma |
|---------------------------------------|----------------------|------------------------|---------------------------|
| Started | 42 | 46 | 58 |
| Completed | 27 | 32 | 42 |
| Not completed | 15 | 14 | 16 |
| Consent withdrawn by subject | 2 | 4 | 5 |
| Physician decision | - | 2 | 1 |
| Adverse event not related to PD | - | - | - |
| Adverse event, non-fatal | 13 | 8 | 9 |
| Death | - | - | 1 |
| Study terminated by sponsor | - | - | - |

| Number of subjects in period 1 | Urothelial carcinoma paclitaxel | Urothelial carcinoma ibrutinib mono | Urothelial carcinoma pembrolizumab |
|---------------------------------------|---------------------------------|-------------------------------------|------------------------------------|
| Started | 63 | 35 | 18 |
| Completed | 43 | 25 | 8 |
| Not completed | 20 | 10 | 10 |
| Consent withdrawn by subject | 8 | 3 | 4 |
| Physician decision | 2 | - | - |
| Adverse event not related to PD | 9 | 5 | 3 |
| Adverse event, non-fatal | - | - | - |
| Death | 1 | 2 | 1 |
| Study terminated by sponsor | - | - | 2 |

Baseline characteristics

Reporting groups

| | |
|--|-------------------------------------|
| Reporting group title | Renal cell carcinoma |
| Reporting group description: | |
| Subjects were to receive ibrutinib PO qd in combination with everolimus (6 hours after ibrutinib) at a dose of 10 mg PO qd in 21-day cycles until unacceptable toxicity or disease progression occurred. If one component of the regimen was discontinued prior to RECIST 1.1 determined disease progression, the other component was to be continued until disease progression or unacceptable toxicity. | |
| Reporting group title | Gastric Adenocarcinoma |
| Reporting group description: | |
| Subjects were to receive ibrutinib administered PO qd in combination with docetaxel at a dose of 60 to 75 mg/sqm administered as a 60-minute IV infusion q3weeks in 21-day cycles until unacceptable toxicity or disease progression occurred. If one component of the regimen was discontinued prior to RECIST 1.1 determined disease progression, the other component was to be continued until disease progression or unacceptable toxicity. | |
| Reporting group title | Colorectal Adenocarcinoma |
| Reporting group description: | |
| Subjects were to receive ibrutinib administered PO qd in combination with cetuximab at a dose of 400 mg/sqm administered initially as a 120-minute IV infusion, then weekly 250 mg/sqm IV over 60 minutes in 21-day cycles until unacceptable toxicity or disease progression occurred. If one component of the regimen was discontinued prior to RECIST 1.1 determined disease progression, the other component was to be continued until disease progression or unacceptable toxicity. | |
| Reporting group title | Urothelial carcinoma paclitaxel |
| Reporting group description: | |
| In Phase 1b, patients in Cohort 2 (UC) were treated first with Ibrutinib 560 mg PO qd and Paclitaxel 80 mg/m ² IV, once weekly in continual 3 weekly cycles (4 patients) followed by Ibrutinib 840 mg and the same dose of Paclitaxel (10 patients). In Phase 2, 49 additional patients were treated with Ibrutinib 840 mg PO qd and Paclitaxel 80 mg/m ² IV. Treatment was given until disease progression or unacceptable toxicity. If one component of the regimen was discontinued prior to RECIST 1.1 determined disease progression, the other component was to be continued until disease progression or unacceptable toxicity. | |
| Reporting group title | Urothelial carcinoma ibrutinib mono |
| Reporting group description: | |
| Monotherapy with ibrutinib 840 mg daily until treatment progression or unacceptable toxicity. | |
| Reporting group title | Urothelial carcinoma pembrolizumab |
| Reporting group description: | |
| Patients were treated with Ibrutinib 560 mg PO qd and pembrolizumab 200 mg as 30 min intravenous infusion, once weekly in continual 3 weekly cycles Treatment was given until disease progression or unacceptable toxicity. If one component of the regimen was discontinued prior to RECIST 1.1 determined disease progression, the other component was to be continued until disease progression or unacceptable toxicity. | |

| Reporting group values | Renal cell carcinoma | Gastric Adenocarcinoma | Colorectal Adenocarcinoma |
|------------------------|----------------------|------------------------|---------------------------|
| Number of subjects | 42 | 46 | 58 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 24 | 33 | 31 |
| From 65-84 years | 18 | 13 | 27 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Units: years | | | |
| median | 62 | 58 | 62 |
| full range (min-max) | 40 to 81 | 35 to 77 | 32 to 81 |

| | | | |
|---------------------------------------|----|----|----|
| Gender categorical Units: Subjects | | | |
| Female | 9 | 12 | 28 |
| Male | 33 | 34 | 30 |

| Reporting group values | Urothelial carcinoma paclitaxel | Urothelial carcinoma ibrutinib mono | Urothelial carcinoma pembrolizumab |
|---------------------------------------|------------------------------------|--|---------------------------------------|
| Number of subjects | 63 | 35 | 18 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 24 | 11 | 6 |
| From 65-84 years | 36 | 22 | 12 |
| 85 years and over | 3 | 2 | 0 |
| Age continuous Units: years | | | |
| median | 68 | 71 | 70 |
| full range (min-max) | 48 to 90 | 52 to 88 | 52 to 84 |
| Gender categorical Units: Subjects | | | |
| Female | 8 | 9 | 5 |
| Male | 55 | 26 | 13 |

| Reporting group values | Total | | |
|---------------------------------------|-------|--|--|
| Number of subjects | 262 | | |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 129 | | |
| From 65-84 years | 128 | | |
| 85 years and over | 5 | | |
| Age continuous Units: years | | | |
| median | | | |
| full range (min-max) | - | | |
| Gender categorical Units: Subjects | | | |
| Female | 71 | | |
| Male | 191 | | |

Subject analysis sets

| | |
|--|---|
| Subject analysis set title | Cohort 1: RCC subjects treated with 560 mg ibr + everolimus |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Participants with RCC received ibrutinib 560 mg QD in combination with everolimus 10 mg QD in Phase 1b. | |
| Subject analysis set title | Cohort 4: CRC subjects treated with 560 mg ibr + cetuximab |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Participants with CRC received ibrutinib 560 mg QD in combination with cetuximab 400 mg/m ² administered as a 120-minute IV infusion. Subsequent weekly dose (all other infusions) was 250 mg/m ² infused over 60 minutes Phase 1b. | |
| Subject analysis set title | Cohort 1: RCC subjects treated with 840 mg ibr + everolimus |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Participants with RCC received ibrutinib 840 mg QD in combination with everolimus 10 mg QD in Phase 1b.

| | |
|----------------------------|---|
| Subject analysis set title | Cohort 3: GC subjects treated with 560 mg ibr + docetaxel |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Participants with GA received ibrutinib 560 mg QD in combination with docetaxel administered as a 60 minute infusion (± 10 minutes) at a dose level of 60 - 75 mg/m², given continually in 21 day cycles Phase 1b.

| | |
|----------------------------|--|
| Subject analysis set title | Cohort 4: CRC subjects treated with 840 mg ibr + cetuximab |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Participants with CRC received ibrutinib 840 mg QD in combination with cetuximab 400 mg/m² administered as a 120-minute IV infusion. Subsequent weekly dose (all other infusions) was 250 mg/m² infused over 60 minutes Phase 1b.

| | |
|----------------------------|--|
| Subject analysis set title | Cohort 2: UC subjects treated with 560 mg ibr + paclitaxel |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Participants with UC received ibrutinib 560 mg QD in combination with paclitaxel 80 mg/m², once weekly, in continual 3 weekly cycles in Phase 1b.

| | |
|----------------------------|--|
| Subject analysis set title | Cohort 5: UC subjects treated with 840 mg ibrutinib mono |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Participants with UC received monotherapy with ibrutinib 840 mg QD.

| | |
|----------------------------|---|
| Subject analysis set title | Cohort 6: UC subjects treated with 840 mg ibr + pembrolizumab |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Participants with UC received ibrutinib 560 mg QD in combination with pembrolizumab 200 mg IV every 3 weeks.

| | |
|----------------------------|--|
| Subject analysis set title | Cohort 2: UC subjects treated with 840 mg ibr + paclitaxel |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Participants with UC received ibrutinib 840 mg QD in combination with paclitaxel 80 mg/m², once weekly, in continual 3 weekly cycles.

| Reporting group values | Cohort 1: RCC subjects treated with 560 mg ibr + everolimus | Cohort 4: CRC subjects treated with 560 mg ibr + cetuximab | Cohort 1: RCC subjects treated with 840 mg ibr + everolimus |
|---------------------------------------|---|--|---|
| Number of subjects | 3 | 8 | 39 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 1 | 6 | 23 |
| From 65-84 years | 2 | 2 | 16 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous Units: years | | | |
| median | 67 | 54.5 | 62 |
| full range (min-max) | 61 to 72 | 35 to 77 | 40 to 81 |
| Gender categorical Units: Subjects | | | |
| Female | 1 | 7 | 8 |
| Male | 2 | 1 | 31 |

| Reporting group values | Cohort 3: GC subjects treated with 560 mg ibr + docetaxel | Cohort 4: CRC subjects treated with 840 mg ibr + cetuximab | Cohort 2: UC subjects treated with 560 mg ibr + paclitaxel |
|---------------------------------------|---|--|--|
| Number of subjects | 46 | 50 | 4 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 33 | 25 | 3 |
| From 65-84 years | 13 | 25 | 1 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous Units: years | | | |
| median | 58 | 64 | 56.5 |
| full range (min-max) | 35 to 77 | 32 to 81 | 48 to 69 |
| Gender categorical Units: Subjects | | | |
| Female | 12 | 21 | 0 |
| Male | 34 | 29 | 4 |

| Reporting group values | Cohort 5: UC subjects treated with 840 mg ibrutinib mono | Cohort 6: UC subjects treated with 840 mg ibr + pembrolizumab | Cohort 2: UC subjects treated with 840 mg ibr + paclitaxel |
|---------------------------------------|--|---|--|
| Number of subjects | 35 | 18 | 59 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 11 | 6 | 21 |
| From 65-84 years | 22 | 12 | 35 |
| 85 years and over | 2 | 0 | 3 |
| Age continuous Units: years | | | |
| median | 71 | 70 | 68.0 |
| full range (min-max) | 52 to 88 | 52 to 84 | 48 to 90 |
| Gender categorical Units: Subjects | | | |
| Female | 9 | 5 | |
| Male | 26 | 13 | |

End points

End points reporting groups

| | |
|--|---|
| Reporting group title | Renal cell carcinoma |
| Reporting group description: | |
| Subjects were to receive ibrutinib PO qd in combination with everolimus (6 hours after ibrutinib) at a dose of 10 mg PO qd in 21-day cycles until unacceptable toxicity or disease progression occurred. If one component of the regimen was discontinued prior to RECIST 1.1 determined disease progression, the other component was to be continued until disease progression or unacceptable toxicity. | |
| Reporting group title | Gastric Adenocarcinoma |
| Reporting group description: | |
| Subjects were to receive ibrutinib administered PO qd in combination with docetaxel at a dose of 60 to 75 mg/sqm administered as a 60-minute IV infusion q3weeks in 21-day cycles until unacceptable toxicity or disease progression occurred. If one component of the regimen was discontinued prior to RECIST 1.1 determined disease progression, the other component was to be continued until disease progression or unacceptable toxicity. | |
| Reporting group title | Colorectal Adenocarcinoma |
| Reporting group description: | |
| Subjects were to receive ibrutinib administered PO qd in combination with cetuximab at a dose of 400 mg/sqm administered initially as a 120-minute IV infusion, then weekly 250 mg/sqm IV over 60 minutes in 21-day cycles until unacceptable toxicity or disease progression occurred. If one component of the regimen was discontinued prior to RECIST 1.1 determined disease progression, the other component was to be continued until disease progression or unacceptable toxicity. | |
| Reporting group title | Urothelial carcinoma paclitaxel |
| Reporting group description: | |
| In Phase 1b, patients in Cohort 2 (UC) were treated first with Ibrutinib 560 mg PO qd and Paclitaxel 80 mg/m ² IV, once weekly in continual 3 weekly cycles (4 patients) followed by Ibrutinib 840 mg and the same dose of Paclitaxel (10 patients). In Phase 2, 49 additional patients were treated with Ibrutinib 840 mg PO qd and Paclitaxel 80 mg/m ² IV. Treatment was given until disease progression or unacceptable toxicity. If one component of the regimen was discontinued prior to RECIST 1.1 determined disease progression, the other component was to be continued until disease progression or unacceptable toxicity. | |
| Reporting group title | Urothelial carcinoma ibrutinib mono |
| Reporting group description: | |
| Monotherapy with ibrutinib 840 mg daily until treatment progression or unacceptable toxicity. | |
| Reporting group title | Urothelial carcinoma pembrolizumab |
| Reporting group description: | |
| Patients were treated with Ibrutinib 560 mg PO qd and pembrolizumab 200 mg as 30 min intravenous infusion, once weekly in continual 3 weekly cycles Treatment was given until disease progression or unacceptable toxicity. If one component of the regimen was discontinued prior to RECIST 1.1 determined disease progression, the other component was to be continued until disease progression or unacceptable toxicity. | |
| Subject analysis set title | Cohort 1: RCC subjects treated with 560 mg ibr + everolimus |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Participants with RCC received ibrutinib 560 mg QD in combination with everolimus 10 mg QD in Phase 1b. | |
| Subject analysis set title | Cohort 4: CRC subjects treated with 560 mg ibr + cetuximab |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Participants with CRC received ibrutinib 560 mg QD in combination with cetuximab 400 mg/m ² administered as a 120-minute IV infusion. Subsequent weekly dose (all other infusions) was 250 mg/m ² infused over 60 minutes Phase 1b. | |
| Subject analysis set title | Cohort 1: RCC subjects treated with 840 mg ibr + everolimus |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Participants with RCC received ibrutinib 840 mg QD in combination with everolimus 10 mg QD in Phase 1b. | |

| | |
|--|---|
| Subject analysis set title | Cohort 3: GC subjects treated with 560 mg ibr + docetaxel |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Participants with GA received ibrutinib 560 mg QD in combination with docetaxel administered as a 60 minute infusion (± 10 minutes) at a dose level of 60 - 75 mg/m ² , given continually in 21 day cycles Phase 1b. | |
| Subject analysis set title | Cohort 4: CRC subjects treated with 840 mg ibr + cetuximab |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Participants with CRC received ibrutinib 840 mg QD in combination with cetuximab 400 mg/m ² administered as a 120-minute IV infusion. Subsequent weekly dose (all other infusions) was 250 mg/m ² infused over 60 minutes Phase 1b. | |
| Subject analysis set title | Cohort 2: UC subjects treated with 560 mg ibr + paclitaxel |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Participants with UC received ibrutinib 560 mg QD in combination with paclitaxel 80 mg/m ² , once weekly, in continual 3 weekly cycles in Phase 1b. | |
| Subject analysis set title | Cohort 5: UC subjects treated with 840 mg ibrutinib mono |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Participants with UC received monotherapy with ibrutinib 840 mg QD. | |
| Subject analysis set title | Cohort 6: UC subjects treated with 840 mg ibr + pembrolizumab |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Participants with UC received ibrutinib 560 mg QD in combination with pembrolizumab 200 mg IV every 3 weeks. | |
| Subject analysis set title | Cohort 2: UC subjects treated with 840 mg ibr + paclitaxel |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Participants with UC received ibrutinib 840 mg QD in combination with paclitaxel 80 mg/m ² , once weekly, in continual 3 weekly cycles. | |

Primary: Progression Free Survival (PFS)

| | |
|--|--|
| End point title | Progression Free Survival (PFS) ^[1] |
| End point description: PFS was defined as the time from the date of first dose of study treatment to the date of first documentation of progressive disease or date of death from any cause, whichever occurs first, regardless of the use of subsequent anti-cancer treatment. PFS was primary endpoint for the combined Phase 1b/2 RP2D analyses in the RCC and UC Ibrutinib + paclitaxel arms and secondary endpoint in the GC, CRC, UC ibrutinib monotherapy arm, and the UC ibrutinib + pembrolizumab arms. The evaluations are based on the efficacy evaluable population treated with the RP2D. Due to limitation of the system, data is only provided for treatment arms for which 90% CIs could be calculated. | |
| End point type | Primary |
| End point timeframe: Results were collected on an ongoing basis with a median time on study in the RCC arm of 37.4/22.5 mo (P1/P2), in the GC arm of 25.3 /11.1 mo (P1/P2), in the CRC arm of 34.1/22.1 mo (P1/P2) and ranging from 10.4 to 37.6 mo in the 3 UC cohorts. | |
| 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: Phase 1b/2 study not powered to show any statistical significant results. No statistical analyses performed. | |

| End point values | Cohort 1: RCC subjects treated with 840 mg ibr + everolimus | Cohort 3: GC subjects treated with 560 mg ibr + docetaxel | Cohort 4: CRC subjects treated with 840 mg ibr + cetuximab | Cohort 5: UC subjects treated with 840 mg ibrutinib mono |
|----------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 36 ^[2] | 39 ^[3] | 47 ^[4] | 29 ^[5] |
| Units: months | | | | |
| number (confidence interval 90%) | 5.6 (3.9 to 7.5) | 4.0 (2.7 to 4.2) | 5.4 (4.1 to 5.8) | 1.6 (1.4 to 2.5) |

Notes:

[2] - Efficacy evaluable population

[3] - Efficacy evaluable population

[4] - Efficacy evaluable population

[5] - Efficacy evaluable population

| End point values | Cohort 2: UC subjects treated with 840 mg ibr + paclitaxel | | | |
|----------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 57 ^[6] | | | |
| Units: months | | | | |
| number (confidence interval 90%) | 4.1 (2.7 to 4.4) | | | |

Notes:

[6] - Efficacy evaluable population

Statistical analyses

No statistical analyses for this end point

Primary: Overall Response Rate (ORR)

| | |
|-----------------|--|
| End point title | Overall Response Rate (ORR) ^[7] |
|-----------------|--|

End point description:

ORR was defined as the proportion of subjects achieving complete response (CR) or partial response (PR) with confirmation based on the best overall response (BOR) per RECIST 1.1 guidelines recorded since date of first dose of study treatment until first documentation of progressive disease or initiation of subsequent anti-cancer treatment, whichever occurs first. Confirmation of CR or PR required two consecutive assessments that are at least 28 days apart.

ORR was primary endpoint in the GC, CRC RCC, UC ibrutinib monotherapy arm, and the UC ibrutinib + pembrolizumab arms and secondary endpoint in the UC Ibrutinib + paclitaxel arm . The evaluations are based on the efficacy evaluable population.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Results were collected on an ongoing basis with a median time on study in the RCC arm of 37.4/22.5 mo (P1/P2), in the GC arm of 25.3 /11.1 mo (P1/P2), in the CRC arm of 34.1/22.1 mo (P1/P2) and ranging from 10.4 to 37.6 mo in the 3 UC cohorts.

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Phase 1b/2 study not powered to show any statistical significant results. No statistical analyses performed.

| End point values | Cohort 1: RCC subjects treated with 840 mg ibr + everolimus | Cohort 3: GC subjects treated with 560 mg ibr + docetaxel | Cohort 4: CRC subjects treated with 840 mg ibr + cetuximab | Cohort 5: UC subjects treated with 840 mg ibrutinib mono |
|----------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 36 ^[8] | 39 ^[9] | 47 ^[10] | 29 ^[11] |
| Units: percent | | | | |
| number (confidence interval 90%) | 2.8 (0.1 to 12.5) | 17.9 (8.7 to 31.1) | 14.9 (7.2 to 26.2) | 6.9 (1.2 to 20.2) |

Notes:

[8] - Efficacy evaluable population

[9] - Efficacy evaluable population

[10] - Efficacy evaluable population

[11] - Efficacy evaluable population

| End point values | Cohort 6: UC subjects treated with 840 mg ibr + pembrolizumab | Cohort 2: UC subjects treated with 840 mg ibr + paclitaxel | | |
|----------------------------------|---|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 14 ^[12] | 57 ^[13] | | |
| Units: percent | | | | |
| number (confidence interval 90%) | 35.7 (15.3 to 61.0) | 26.3 (17.0 to 37.6) | | |

Notes:

[12] - Efficacy evaluable population

[13] - Efficacy evaluable population

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

| | |
|-----------------|----------------------------|
| End point title | Disease Control Rate (DCR) |
|-----------------|----------------------------|

End point description:

DCR was defined as the proportion of subjects achieving CR, PR, or stable disease of length ≥ 6 weeks based on the BOR per RECIST 1.1 guidelines recorded since date of first dose of study treatment until first documentation of progressive disease or initiation of subsequent anti-cancer treatment, whichever occurs first. Confirmation of CR or PR was not required.

DCR was primary endpoint in the GC, CRC RCC, UC ibrutinib monotherapy arm, and the UC ibrutinib + pembrolizumab arms and secondary endpoint in the UC Ibrutinib + paclitaxel arm . The evaluations are based on the efficacy evaluable population.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Results were collected on an ongoing basis with a median time on study in the RCC arm of 37.4/22.5 mo (P1/P2), in the GC arm of 25.3 /11.1 mo (P1/P2), in the CRC arm of 34.1/22.1 mo (P1/P2) and ranging from 10.4 to 37.6 mo in the 3 UC cohorts.

| End point values | Cohort 1: RCC subjects treated with 840 mg ibr + everolimus | Cohort 3: GC subjects treated with 560 mg ibr + docetaxel | Cohort 4: CRC subjects treated with 840 mg ibr + cetuximab | Cohort 5: UC subjects treated with 840 mg ibrutinib mono |
|----------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 36 ^[14] | 39 ^[15] | 47 ^[16] | 29 ^[17] |
| Units: percent | | | | |
| number (confidence interval 90%) | 80.6 (66.6 to 90.5) | 74.4 (60.4 to 85.4) | 83.0 (71.4 to 91.2) | 48.3 (32.0 to 64.8) |

Notes:

[14] - Efficacy evaluable population

[15] - Efficacy evaluable population

[16] - Efficacy evaluable population

[17] - Efficacy evaluable population

| End point values | Cohort 6: UC subjects treated with 840 mg ibr + pembrolizumab | Cohort 2: UC subjects treated with 840 mg ibr + paclitaxel | | |
|----------------------------------|---|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 14 ^[18] | 57 ^[19] | | |
| Units: percent | | | | |
| number (confidence interval 90%) | 71.4 (46.0 to 89.6) | 66.7 (55.0 to 77.0) | | |

Notes:

[18] - Efficacy evaluable population

[19] - Efficacy evaluable population

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

| | |
|-----------------|-----------------------|
| End point title | Overall Survival (OS) |
|-----------------|-----------------------|

End point description:

OS was defined as the time from the date of first dose of study treatment to the date of death from any cause.

The evaluations are based on the efficacy evaluable population treated with the RP2D.

Due to limitation of the system, data is only provided for treatment arms for which 90% CIs could be calculated.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Results were collected on an ongoing basis with a median time on study in the RCC arm of 37.4/22.5 mo (P1/P2), in the GC arm of 25.3 /11.1 mo (P1/P2), in the CRC arm of 34.1/22.1 mo (P1/P2) and ranging from 10.4 to 37.6 mo in the 3 UC cohorts.

| End point values | Cohort 1: RCC subjects treated with 840 mg ibr + everolimus | Cohort 3: GC subjects treated with 560 mg ibr + docetaxel | Cohort 4: CRC subjects treated with 840 mg ibr + cetuximab | Cohort 2: UC subjects treated with 840 mg ibr + paclitaxel |
|----------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 36 ^[20] | 39 ^[21] | 47 ^[22] | 57 ^[23] |
| Units: months | | | | |
| number (confidence interval 90%) | 21.0 (13.1 to 25.3) | 7.3 (5.5 to 9.6) | 15.0 (10.5 to 17.2) | 8.2 (1.0 to 44.7) |

Notes:

[20] - Efficacy evaluable population

[21] - Efficacy evaluable population

[22] - Efficacy evaluable population

[23] - Efficacy evaluable population

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

| | |
|-----------------|----------------------------|
| End point title | Duration of Response (DOR) |
|-----------------|----------------------------|

End point description:

DOR was defined for confirmed responders (PR or better) as the time from the date of initial response (PR or better) to the date of first documentation of progressive disease or death, whichever occurs first, regardless of use of subsequent anti-cancer treatment. Confirmed responders without documentation of progressive disease or death or with unknown status at the data extract were censored at the last adequate post-baseline disease assessment showing no evidence of progressive disease.

Due to limitation of the system, data is only provided for treatment arms for which 90% CIs could be calculated.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Results were collected on an ongoing basis with a median time on study in the RCC arm of 37.4/22.5 mo (P1/P2), in the GC arm of 25.3 /11.1 mo (P1/P2), in the CRC arm of 34.1/22.1 mo (P1/P2) and ranging from 10.4 to 37.6 mo in the 3 UC cohorts.

| End point values | Cohort 1: RCC subjects treated with 840 mg ibr + everolimus | Cohort 3: GC subjects treated with 560 mg ibr + docetaxel | Cohort 4: CRC subjects treated with 840 mg ibr + cetuximab | Cohort 2: UC subjects treated with 840 mg ibr + paclitaxel |
|----------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 1 ^[24] | 7 ^[25] | 7 ^[26] | 15 ^[27] |
| Units: months | | | | |
| number (confidence interval 90%) | 3.1 (3.1 to 3.1) | 5.5 (3.0 to 18.0) | 11.1 (4.2 to 12.5) | 4.4 (3.1 to 6.8) |

Notes:

[24] - For patients having a response.

[25] - For patients having a response.

[26] - For patients having a response.

[27] - For patients having a response.

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to 30 days after the last dose of study drug or the day before initiation of subsequent anti-cancer treatment, whichever comes first.

Adverse event reporting additional description:

Note: for non-serious AEs a cutoff of 5% has been used for each individual safety reporting group below. Frequency and number of events was not available for non-serious AEs for all reporting group, i.e. a frequency of "0" for a non-serious AE thus means that the frequency of this AE was lower than 5%.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 22.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | Subjects treated with RP2D in Cohorts 1, 3, and 4 |
|-----------------------|---|

Reporting group description:

Safety is reported here for all subjects treated with the RP2D regardless of the indication for Cohorts 1, 3 and 4 (RCC, GC, CRC). Safety of subjects treated with lower ibrutinib doses in the Phase I part of the study are not reported due to the low number of subjects.

| | |
|-----------------------|--|
| Reporting group title | Cohort 2: UC Subjects treated with 840 mg ibr + paclitaxel |
|-----------------------|--|

Reporting group description:

Safety is reported here for all UC subjects treated in Cohort 2 with the RP2D of 840 mg ibrutinib. Safety of subjects treated with lower ibrutinib doses in the Phase I part of the study are not reported due to the low number of subjects.

| | |
|-----------------------|--|
| Reporting group title | Cohort 5: UC Subjects treated with 840 mg ibr mono |
|-----------------------|--|

Reporting group description:

Safety is reported here for all UC subjects treated in Cohort 5 with the RP2D of 840 mg ibrutinib as monotherapy. No patients have been treated with a lower dose in this cohort.

| | |
|-----------------------|---|
| Reporting group title | Cohort 6: UC Subjects treated with 560 mg ibr + pembrolizumab |
|-----------------------|---|

Reporting group description:

Safety is reported here for all UC subjects treated in Cohort 6 with the RP2D of 560 mg ibrutinib. No subjects have been treated with a lower dose.

| Serious adverse events | Subjects treated with RP2D in Cohorts 1, 3, and 4 | Cohort 2: UC Subjects treated with 840 mg ibr + paclitaxel | Cohort 5: UC Subjects treated with 840 mg ibr mono |
|---|---|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 62 / 135 (45.93%) | 36 / 59 (61.02%) | 19 / 35 (54.29%) |
| number of deaths (all causes) | 88 | 22 | 22 |
| number of deaths resulting from adverse events | 7 | 7 | 7 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma gastric | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 |

| | | | |
|---|-----------------|----------------|----------------|
| Colorectal adenocarcinoma | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 cancer | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Metastases to central nervous system | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 1 / 59 (1.69%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to spine | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Renal cell carcinoma | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Transitional cell carcinoma | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 2 / 59 (3.39%) | 2 / 35 (5.71%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |

| | | | |
|--|-----------------|----------------|----------------|
| Hypertension | | | |
| subjects affected / exposed | 2 / 135 (1.48%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Aortic stenosis | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Surgical and medical procedures | | | |
| Pleurodesis | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 4 / 135 (2.96%) | 2 / 59 (3.39%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 2 / 5 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Generalised oedema | | | |
| subjects affected / exposed | 2 / 135 (1.48%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Chest pain | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 |

| | | | |
|---|-----------------|----------------|----------------|
| Pyrexia | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 3 / 59 (5.08%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 3 / 59 (5.08%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| Malaise | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sudden cardiac death | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Sudden death | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Reproductive system and breast disorders | | | |
| Pelvic pain | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 59 (1.69%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 3 / 135 (2.22%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Pleural effusion | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 2 / 135 (1.48%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemoptysis | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 1 / 59 (1.69%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary oedema | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 59 (1.69%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Confusional state | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 59 (1.69%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Blood urine present | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 59 (1.69%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Gun shot wound | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Urinary tract stoma complication | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 59 (1.69%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (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 | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 135 (1.48%) | 1 / 59 (1.69%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 |

| | | | |
|---|-----------------|----------------|----------------|
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 59 (1.69%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleuropericarditis | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute left ventricular failure | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Left ventricular failure | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Pericarditis | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (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 | | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 2 / 135 (1.48%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Cerebral infarction | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Cerebral ischaemia | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Headache | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 1 / 59 (1.69%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Presyncope | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 59 (1.69%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 59 (1.69%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 59 (1.69%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Subarachnoid haemorrhage | | | |

| | | | |
|---|------------------|----------------|----------------|
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (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 | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 11 / 135 (8.15%) | 2 / 59 (3.39%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 8 / 14 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 4 / 135 (2.96%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 3 / 6 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anaemia | | | |
| subjects affected / exposed | 3 / 135 (2.22%) | 0 / 59 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 4 / 5 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 59 (1.69%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 4 / 135 (2.96%) | 1 / 59 (1.69%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 3 / 135 (2.22%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ileus | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 3 / 135 (2.22%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Stomatitis | | | |
| subjects affected / exposed | 3 / 135 (2.22%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ascites | | | |
| subjects affected / exposed | 2 / 135 (1.48%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 135 (1.48%) | 1 / 59 (1.69%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Melaena | | | |
| subjects affected / exposed | 2 / 135 (1.48%) | 1 / 59 (1.69%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 motility disorder | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematemesis | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 135 (0.74%) | 1 / 59 (1.69%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 1 / 59 (1.69%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Obstruction gastric | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Ileus paralytic | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 59 (1.69%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (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 function abnormal | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (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 | 2 / 135 (1.48%) | 2 / 59 (3.39%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 3 / 3 | 1 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematuria | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 2 / 59 (3.39%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Renal Failure | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bladder pain | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 59 (1.69%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urethral stenosis | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 59 (1.69%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal injury | | | |

| | | | |
|--|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Neck mass | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 59 (1.69%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Back pain | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 59 (1.69%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 59 (1.69%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 8 / 135 (5.93%) | 2 / 59 (3.39%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 1 / 9 | 1 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 5 / 135 (3.70%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 4 / 5 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|----------------|----------------|
| Respiratory tract infection | | | |
| subjects affected / exposed | 2 / 135 (1.48%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Sepsis | | | |
| subjects affected / exposed | 2 / 135 (1.48%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 135 (1.48%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Atypical pneumonia | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Biliary tract infection | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 1 / 59 (1.69%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterococcal bacteraemia | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Herpes simplex | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Meningitis aseptic | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Paronychia | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Staphylococcal infection | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 7 / 59 (11.86%) | 2 / 35 (5.71%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 13 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Emphysematous cystitis | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 59 (1.69%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 59 (1.69%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumocystis jirovecii infection | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 59 (1.69%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Pneumonia streptococcal | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 59 (1.69%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 59 (1.69%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 59 (1.69%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Soft tissue infection | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 59 (1.69%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ureteritis | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 59 (1.69%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection bacterial | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 59 (1.69%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 59 (1.69%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Bacteraemia | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COVID-19 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Klebsiella infection | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Dehydration | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 2 / 59 (3.39%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Hyperglycaemia | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 135 (0.74%) | 1 / 59 (1.69%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperphosphataemia | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 59 (0.00%) | 0 / 35 (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 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (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 |

| | | | |
|---|--|--|--|
| Serious adverse events | Cohort 6: UC Subjects treated with 560 mg ibr + pembrolizumab | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 10 / 18 (55.56%) | | |
| number of deaths (all causes) | 7 | | |
| number of deaths resulting from adverse events | 3 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma gastric | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colorectal adenocarcinoma | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastric cancer | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metastases to central nervous system | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metastases to spine | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal cell carcinoma | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transitional cell carcinoma | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aortic stenosis | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |

| | | | |
|--|----------------|--|--|
| Pleurodesis | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Generalised oedema | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 18 (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 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 18 (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 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Malaise | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sudden cardiac death | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sudden death | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Pelvic pain | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia aspiration | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Blood urine present | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Injury, poisoning and procedural complications | | | |
| Gun shot wound | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract stoma complication | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subdural haematoma | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pleuropericarditis | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Acute left ventricular failure subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Left ventricular failure subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pericarditis subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Transient ischaemic attack subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebral haemorrhage subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebral infarction subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebral ischaemia subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Headache subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Presyncope | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Radiculopathy | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutropenia | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 18 (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 | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ileus | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ascites | | | |

| | | | | |
|---|----------------|--|--|--|
| subjects affected / exposed | 0 / 18 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diarrhoea | | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Melaena | | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Abdominal pain upper | | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Colitis | | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal motility disorder | | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haematemesis | | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intestinal obstruction | | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nausea | | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Obstruction gastric | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ileus paralytic | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic function abnormal | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal Failure | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bladder pain | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urethral stenosis | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal injury | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Neck mass | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper respiratory tract infection | | | |

| | | | | |
|---|----------------|--|--|--|
| subjects affected / exposed | 0 / 18 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Appendicitis | | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Atypical pneumonia | | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Biliary tract infection | | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Clostridium difficile infection | | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Enterococcal bacteraemia | | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Herpes simplex | | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lower respiratory tract infection | | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Meningitis aseptic | | | | |

| | | | | |
|---|----------------|--|--|--|
| subjects affected / exposed | 0 / 18 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Paronychia | | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Staphylococcal infection | | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Urinary tract infection | | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Emphysematous cystitis | | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infection | | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumocystis jirovecii infection | | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia streptococcal | | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pyelonephritis | | | | |

| | | | | |
|---|----------------|--|--|--|
| subjects affected / exposed | 1 / 18 (5.56%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Septic shock | | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Soft tissue infection | | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ureteritis | | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Urinary tract infection bacterial | | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Urosepsis | | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bacteraemia | | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| COVID-19 | | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Klebsiella infection | | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperphosphataemia | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyponatraemia | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Subjects treated with RP2D in Cohorts 1, 3, and 4 | Cohort 2: UC Subjects treated with 840 mg ibr + paclitaxel | Cohort 5: UC Subjects treated with 840 mg ibr mono |
|---|---|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 132 / 135 (97.78%) | 59 / 59 (100.00%) | 34 / 35 (97.14%) |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 3 / 59 (5.08%) | 2 / 35 (5.71%) |
| occurrences (all) | 0 | 3 | 3 |
| Jugular vein distension | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pallor | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypertension | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 4 / 59 (6.78%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 8 | 0 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 52 / 135 (38.52%) | 19 / 59 (32.20%) | 10 / 35 (28.57%) |
| occurrences (all) | 120 | 43 | 14 |
| Asthenia | | | |
| subjects affected / exposed | 35 / 135 (25.93%) | 29 / 59 (49.15%) | 12 / 35 (34.29%) |
| occurrences (all) | 91 | 125 | 19 |
| Oedema peripheral | | | |
| subjects affected / exposed | 21 / 135 (15.56%) | 15 / 59 (25.42%) | 6 / 35 (17.14%) |
| occurrences (all) | 29 | 21 | 6 |
| Pyrexia | | | |

| | | | |
|---|-------------------|------------------|----------------|
| subjects affected / exposed | 21 / 135 (15.56%) | 16 / 59 (27.12%) | 3 / 35 (8.57%) |
| occurrences (all) | 27 | 26 | 5 |
| Chills | | | |
| subjects affected / exposed | 7 / 135 (5.19%) | 4 / 59 (6.78%) | 0 / 35 (0.00%) |
| occurrences (all) | 10 | 4 | 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 2 / 35 (5.71%) |
| occurrences (all) | 0 | 0 | 2 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Swelling | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 3 / 59 (5.08%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Immune system disorders | | | |
| Seasonal allergy | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 3 / 59 (5.08%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Reproductive system and breast disorders | | | |
| Vaginal discharge | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Balanoposthitis | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 3 / 59 (5.08%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Epistaxis | | | |
| subjects affected / exposed | 37 / 135 (27.41%) | 9 / 59 (15.25%) | 0 / 35 (0.00%) |
| occurrences (all) | 54 | 11 | 0 |
| Cough | | | |

| | | | |
|-----------------------------|-------------------|-----------------|----------------|
| subjects affected / exposed | 24 / 135 (17.78%) | 5 / 59 (8.47%) | 0 / 35 (0.00%) |
| occurrences (all) | 37 | 5 | 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 12 / 135 (8.89%) | 9 / 59 (15.25%) | 0 / 35 (0.00%) |
| occurrences (all) | 25 | 13 | 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 11 / 135 (8.15%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 13 | 0 | 0 |
| Haemoptysis | | | |
| subjects affected / exposed | 8 / 135 (5.93%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 10 | 0 | 0 |
| Productive cough | | | |
| subjects affected / exposed | 8 / 135 (5.93%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 10 | 0 | 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 2 / 35 (5.71%) |
| occurrences (all) | 0 | 0 | 2 |
| Sputum discoloured | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 3 / 59 (5.08%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 11 / 135 (8.15%) | 6 / 59 (10.17%) | 0 / 35 (0.00%) |
| occurrences (all) | 14 | 6 | 0 |
| Anxiety | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 2 / 35 (5.71%) |
| occurrences (all) | 0 | 0 | 2 |
| Depression | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|--|-------------------------|-----------------------|---------------------|
| Depressed mood subjects affected / exposed occurrences (all) | 0 / 135 (0.00%) 0 | 3 / 59 (5.08%) 3 | 0 / 35 (0.00%) 0 |
| Investigations | | | |
| Weight decreased subjects affected / exposed occurrences (all) | 17 / 135 (12.59%) 21 | 0 / 59 (0.00%) 0 | 3 / 35 (8.57%) 4 |
| Platelet count decreased subjects affected / exposed occurrences (all) | 14 / 135 (10.37%) 19 | 7 / 59 (11.86%) 11 | 0 / 35 (0.00%) 0 |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 11 / 135 (8.15%) 12 | 4 / 59 (6.78%) 10 | 0 / 35 (0.00%) 0 |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | 11 / 135 (8.15%) 24 | 9 / 59 (15.25%) 11 | 0 / 35 (0.00%) 0 |
| Blood creatinine increased subjects affected / exposed occurrences (all) | 10 / 135 (7.41%) 24 | 0 / 59 (0.00%) 0 | 0 / 35 (0.00%) 0 |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 9 / 135 (6.67%) 18 | 0 / 59 (0.00%) 0 | 0 / 35 (0.00%) 0 |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 8 / 135 (5.93%) 9 | 4 / 59 (6.78%) 15 | 0 / 35 (0.00%) 0 |
| Protein urine present subjects affected / exposed occurrences (all) | 0 / 135 (0.00%) 0 | 0 / 59 (0.00%) 0 | 0 / 35 (0.00%) 0 |
| C-reactive protein increased subjects affected / exposed occurrences (all) | 0 / 135 (0.00%) 0 | 0 / 59 (0.00%) 0 | 0 / 35 (0.00%) 0 |
| Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) | 0 / 135 (0.00%) 0 | 0 / 59 (0.00%) 0 | 2 / 35 (5.71%) 4 |
| Blood bilirubin increased | | | |

| | | | |
|--|-------------------|------------------|-----------------|
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood thyroid stimulating hormone increased | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood urea increased | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 2 / 35 (5.71%) |
| occurrences (all) | 0 | 0 | 3 |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 2 / 35 (5.71%) |
| occurrences (all) | 0 | 0 | 2 |
| Contusion | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cardiac disorders | | | |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sinus bradycardia | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 22 / 135 (16.30%) | 10 / 59 (16.95%) | 9 / 35 (25.71%) |
| occurrences (all) | 28 | 15 | 13 |
| Headache | | | |
| subjects affected / exposed | 12 / 135 (8.89%) | 3 / 59 (5.08%) | 3 / 35 (8.57%) |
| occurrences (all) | 16 | 3 | 4 |
| Peripheral sensory neuropathy | | | |

| | | | |
|--------------------------------------|-------------------|------------------|-----------------|
| subjects affected / exposed | 11 / 135 (8.15%) | 15 / 59 (25.42%) | 0 / 35 (0.00%) |
| occurrences (all) | 16 | 31 | 0 |
| Neurotoxicity | | | |
| subjects affected / exposed | 7 / 135 (5.19%) | 10 / 59 (16.95%) | 0 / 35 (0.00%) |
| occurrences (all) | 21 | 32 | 0 |
| Head discomfort | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 5 / 59 (8.47%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 15 | 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 4 / 59 (6.78%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Dysgeusia | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 6 / 59 (10.17%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 10 | 0 |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 4 / 59 (6.78%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 6 | 0 |
| Peripheral sensorimotor neuropathy | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 3 / 59 (5.08%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 6 | 0 |
| Somnolence | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 3 / 59 (5.08%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 51 / 135 (37.78%) | 24 / 59 (40.68%) | 6 / 35 (17.14%) |
| occurrences (all) | 160 | 64 | 12 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 24 / 135 (17.78%) | 5 / 59 (8.47%) | 0 / 35 (0.00%) |
| occurrences (all) | 55 | 10 | 0 |

| | | | |
|------------------------------|-------------------|------------------|------------------|
| Neutropenia | | | |
| subjects affected / exposed | 18 / 135 (13.33%) | 10 / 59 (16.95%) | 0 / 35 (0.00%) |
| occurrences (all) | 46 | 13 | 0 |
| Coagulopathy | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Increased tendency to bruise | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eye disorders | | | |
| Dry eye | | | |
| subjects affected / exposed | 7 / 135 (5.19%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 10 | 0 | 0 |
| Cataract | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vitreous detachment | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 70 / 135 (51.85%) | 43 / 59 (72.88%) | 10 / 35 (28.57%) |
| occurrences (all) | 148 | 106 | 14 |
| Stomatitis | | | |
| subjects affected / exposed | 68 / 135 (50.37%) | 17 / 59 (28.81%) | 3 / 35 (8.57%) |
| occurrences (all) | 154 | 28 | 3 |
| Nausea | | | |
| subjects affected / exposed | 46 / 135 (34.07%) | 23 / 59 (38.98%) | 16 / 35 (45.71%) |
| occurrences (all) | 82 | 37 | 19 |
| Vomiting | | | |

| | | | |
|----------------------------------|-------------------|------------------|------------------|
| subjects affected / exposed | 34 / 135 (25.19%) | 17 / 59 (28.81%) | 10 / 35 (28.57%) |
| occurrences (all) | 55 | 25 | 15 |
| Constipation | | | |
| subjects affected / exposed | 23 / 135 (17.04%) | 19 / 59 (32.20%) | 9 / 35 (25.71%) |
| occurrences (all) | 26 | 21 | 12 |
| Abdominal pain | | | |
| subjects affected / exposed | 18 / 135 (13.33%) | 6 / 59 (10.17%) | 0 / 35 (0.00%) |
| occurrences (all) | 27 | 6 | 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 17 / 135 (12.59%) | 7 / 59 (11.86%) | 2 / 35 (5.71%) |
| occurrences (all) | 20 | 7 | 2 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 13 / 135 (9.63%) | 3 / 59 (5.08%) | 0 / 35 (0.00%) |
| occurrences (all) | 19 | 4 | 0 |
| Dry mouth | | | |
| subjects affected / exposed | 10 / 135 (7.41%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 22 | 0 | 0 |
| Dysphagia | | | |
| subjects affected / exposed | 7 / 135 (5.19%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 9 | 0 | 0 |
| Change of bowel habit | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lip oedema | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lip pain | | | |

| | | | |
|--|--------------------------|------------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 135 (0.00%) 0 | 0 / 59 (0.00%) 0 | 0 / 35 (0.00%) 0 |
| Oral mucosal erythema subjects affected / exposed occurrences (all) | 0 / 135 (0.00%) 0 | 0 / 59 (0.00%) 0 | 0 / 35 (0.00%) 0 |
| Abdominal distension subjects affected / exposed occurrences (all) | 0 / 135 (0.00%) 0 | 0 / 59 (0.00%) 0 | 2 / 35 (5.71%) 2 |
| Haemorrhoids subjects affected / exposed occurrences (all) | 0 / 135 (0.00%) 0 | 3 / 59 (5.08%) 3 | 0 / 35 (0.00%) 0 |
| Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all) | 0 / 135 (0.00%) 0 | 0 / 59 (0.00%) 0 | 0 / 35 (0.00%) 0 |
| Hepatic function abnormal subjects affected / exposed occurrences (all) | 0 / 135 (0.00%) 0 | 0 / 59 (0.00%) 0 | 2 / 35 (5.71%) 4 |
| Skin and subcutaneous tissue disorders Dermatitis acneiform subjects affected / exposed occurrences (all) | 48 / 135 (35.56%) 160 | 7 / 59 (11.86%) 11 | 0 / 35 (0.00%) 0 |
| Pruritus subjects affected / exposed occurrences (all) | 30 / 135 (22.22%) 42 | 4 / 59 (6.78%) 5 | 3 / 35 (8.57%) 3 |
| Dry skin subjects affected / exposed occurrences (all) | 27 / 135 (20.00%) 45 | 7 / 59 (11.86%) 9 | 2 / 35 (5.71%) 2 |
| Rash maculo-papular subjects affected / exposed occurrences (all) | 19 / 135 (14.07%) 71 | 5 / 59 (8.47%) 11 | 2 / 35 (5.71%) 2 |
| Alopecia subjects affected / exposed occurrences (all) | 17 / 135 (12.59%) 20 | 18 / 59 (30.51%) 24 | 0 / 35 (0.00%) 0 |
| Palmar-plantar erythrodysaesthesia syndrome | | | |

| | | | |
|-----------------------------|-------------------|------------------|-----------------|
| subjects affected / exposed | 16 / 135 (11.85%) | 6 / 59 (10.17%) | 0 / 35 (0.00%) |
| occurrences (all) | 38 | 6 | 0 |
| Petechiae | | | |
| subjects affected / exposed | 9 / 135 (6.67%) | 0 / 59 (0.00%) | 5 / 35 (14.29%) |
| occurrences (all) | 17 | 0 | 6 |
| Rash erythematous | | | |
| subjects affected / exposed | 9 / 135 (6.67%) | 4 / 59 (6.78%) | 2 / 35 (5.71%) |
| occurrences (all) | 12 | 6 | 4 |
| Rash | | | |
| subjects affected / exposed | 8 / 135 (5.93%) | 6 / 59 (10.17%) | 0 / 35 (0.00%) |
| occurrences (all) | 10 | 7 | 0 |
| Hyperhidrosis | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Night sweats | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Purpura | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Seborrhoeic dermatitis | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urticaria | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Renal and urinary disorders | | | |
| Proteinuria | | | |
| subjects affected / exposed | 9 / 135 (6.67%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 18 | 0 | 0 |
| Haematuria | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 12 / 59 (20.34%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 18 | 0 |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 3 / 35 (8.57%) |
| occurrences (all) | 0 | 0 | 4 |

| | | | |
|---|-------------------|------------------|----------------|
| Dysuria | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 3 / 59 (5.08%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Renal impairment | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 4 / 59 (6.78%) | 2 / 35 (5.71%) |
| occurrences (all) | 0 | 12 | 3 |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 16 / 135 (11.85%) | 12 / 59 (20.34%) | 2 / 35 (5.71%) |
| occurrences (all) | 27 | 20 | 3 |
| Back pain | | | |
| subjects affected / exposed | 13 / 135 (9.63%) | 10 / 59 (16.95%) | 2 / 35 (5.71%) |
| occurrences (all) | 14 | 12 | 2 |
| Myalgia | | | |
| subjects affected / exposed | 12 / 135 (8.89%) | 8 / 59 (13.56%) | 2 / 35 (5.71%) |
| occurrences (all) | 16 | 9 | 2 |
| Pain in extremity | | | |
| subjects affected / exposed | 9 / 135 (6.67%) | 5 / 59 (8.47%) | 3 / 35 (8.57%) |
| occurrences (all) | 14 | 6 | 4 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 7 / 135 (5.19%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 8 | 0 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscular weakness | | | |

| | | | |
|-----------------------------|-------------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 135 (0.00%) | 4 / 59 (6.78%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Flank pain | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bone pain | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infections and infestations | | | |
| Paronychia | | | |
| subjects affected / exposed | 29 / 135 (21.48%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 54 | 0 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 11 / 135 (8.15%) | 6 / 59 (10.17%) | 5 / 35 (14.29%) |
| occurrences (all) | 13 | 10 | 5 |
| Conjunctivitis | | | |
| subjects affected / exposed | 9 / 135 (6.67%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 13 | 0 | 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fungal infection | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Herpes virus infection | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash pustular | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 59 (0.00%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|-------------------------|------------------------|------------------------|
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 135 (0.00%) 0 | 0 / 59 (0.00%) 0 | 0 / 35 (0.00%) 0 |
| Respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 135 (0.00%) 0 | 3 / 59 (5.08%) 3 | 0 / 35 (0.00%) 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 50 / 135 (37.04%) 92 | 25 / 59 (42.37%) 50 | 12 / 35 (34.29%) 15 |
| Hypokalaemia subjects affected / exposed occurrences (all) | 18 / 135 (13.33%) 33 | 7 / 59 (11.86%) 9 | 0 / 35 (0.00%) 0 |
| Hypomagnesaemia subjects affected / exposed occurrences (all) | 16 / 135 (11.85%) 35 | 6 / 59 (10.17%) 10 | 3 / 35 (8.57%) 4 |
| Dehydration subjects affected / exposed occurrences (all) | 8 / 135 (5.93%) 9 | 0 / 59 (0.00%) 0 | 0 / 35 (0.00%) 0 |
| Hypocalcaemia subjects affected / exposed occurrences (all) | 8 / 135 (5.93%) 14 | 0 / 59 (0.00%) 0 | 0 / 35 (0.00%) 0 |
| Hypophosphataemia subjects affected / exposed occurrences (all) | 8 / 135 (5.93%) 12 | 0 / 59 (0.00%) 0 | 0 / 35 (0.00%) 0 |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 7 / 135 (5.19%) 21 | 0 / 59 (0.00%) 0 | 0 / 35 (0.00%) 0 |
| Hyperuricaemia subjects affected / exposed occurrences (all) | 0 / 135 (0.00%) 0 | 0 / 59 (0.00%) 0 | 0 / 35 (0.00%) 0 |
| Gout subjects affected / exposed occurrences (all) | 0 / 135 (0.00%) 0 | 0 / 59 (0.00%) 0 | 0 / 35 (0.00%) 0 |
| Hyponatraemia | | | |

| | | | |
|-----------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 135 (0.00%) | 4 / 59 (6.78%) | 4 / 35 (11.43%) |
| occurrences (all) | 0 | 4 | 8 |

| | | | |
|--|--|--|--|
| Non-serious adverse events | Cohort 6: UC Subjects treated with 560 mg ibr + pembrolizumab | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 17 / 18 (94.44%) | | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Jugular vein distension | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Pallor | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences (all) | 0 | | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 8 / 18 (44.44%) | | |
| occurrences (all) | 15 | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 3 / 18 (16.67%) | | |
| occurrences (all) | 5 | | |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 18 (16.67%) | | |
| occurrences (all) | 3 | | |
| Chills | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|---|----------------------|--|--|
| Influenza like illness subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | | |
| Non-cardiac chest pain subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | | |
| Swelling subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | | |
| Gait disturbance subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | | |
| Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | | |
| Reproductive system and breast disorders Vaginal discharge subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 2 | | |
| Balanoposthitis subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | | |
| Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all) | 2 / 18 (11.11%) 2 | | |
| Cough subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | | |
| Dyspnoea subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | | |

| | | | |
|-----------------------------|-----------------|--|--|
| Oropharyngeal pain | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences (all) | 2 | | |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences (all) | 0 | | |
| Productive cough | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences (all) | 0 | | |
| Sputum discoloured | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences (all) | 0 | | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences (all) | 2 | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Depression | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 2 | | |
| Depressed mood | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences (all) | 0 | | |
| Investigations | | | |

| | | | |
|---|-----------------|--|--|
| Weight decreased | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 3 / 18 (16.67%) | | |
| occurrences (all) | 3 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences (all) | 0 | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences (all) | 0 | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Protein urine present | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| C-reactive protein increased | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences (all) | 2 | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 3 | | |
| Blood thyroid stimulating hormone increased | | | |

| | | | |
|--|---|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Blood urea increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hypoalbuminaemia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 18 (5.56%)</p> <p>2</p> <p>1 / 18 (5.56%)</p> <p>2</p> <p>0 / 18 (0.00%)</p> <p>0</p> | | |
| <p>Injury, poisoning and procedural complications</p> <p>Fall</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Contusion</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Post procedural haemorrhage</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>3 / 18 (16.67%)</p> <p>4</p> <p>1 / 18 (5.56%)</p> <p>1</p> <p>1 / 18 (5.56%)</p> <p>1</p> | | |
| <p>Cardiac disorders</p> <p>Pericardial effusion</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Sinus bradycardia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 18 (5.56%)</p> <p>1</p> <p>1 / 18 (5.56%)</p> <p>1</p> | | |
| <p>Nervous system disorders</p> <p>Dizziness</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Headache</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Peripheral sensory neuropathy</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Neurotoxicity</p> | <p>4 / 18 (22.22%)</p> <p>4</p> <p>1 / 18 (5.56%)</p> <p>1</p> <p>1 / 18 (5.56%)</p> <p>1</p> | | |

| | | | |
|--------------------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences (all) | 0 | | |
| Head discomfort | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Dysgeusia | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences (all) | 0 | | |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences (all) | 0 | | |
| Peripheral sensorimotor neuropathy | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences (all) | 0 | | |
| Somnolence | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences (all) | 0 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 3 | | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|---|----------------------|--|--|
| Coagulopathy subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | | |
| Increased tendency to bruise subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | | |
| Iron deficiency anaemia subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | | |
| Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | | |
| Eye disorders Dry eye subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | | |
| Cataract subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | | |
| Vitreous detachment subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | | |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) | 8 / 18 (44.44%) 8 | | |
| Stomatitis subjects affected / exposed occurrences (all) | 4 / 18 (22.22%) 8 | | |
| Nausea subjects affected / exposed occurrences (all) | 6 / 18 (33.33%) 7 | | |
| Vomiting subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | | |
| Constipation | | | |

| | | | |
|----------------------------------|-----------------|--|--|
| subjects affected / exposed | 7 / 18 (38.89%) | | |
| occurrences (all) | 7 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences (all) | 0 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dry mouth | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences (all) | 2 | | |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences (all) | 0 | | |
| Change of bowel habit | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Lip oedema | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Lip pain | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Oral mucosal erythema | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences (all) | 0 | | |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hepatobiliary disorders | | | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences (all) | 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pruritus | | | |
| subjects affected / exposed | 3 / 18 (16.67%) | | |
| occurrences (all) | 3 | | |
| Dry skin | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences (all) | 2 | | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 5 / 18 (27.78%) | | |
| occurrences (all) | 12 | | |
| Alopecia | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences (all) | 0 | | |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences (all) | 0 | | |
| Petechiae | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rash erythematous | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Rash | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hyperhidrosis | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Night sweats | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Purpura | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Seborrhoeic dermatitis | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Urticaria | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Renal and urinary disorders | | | |
| Proteinuria | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences (all) | 0 | | |
| Haematuria | | | |
| subjects affected / exposed | 5 / 18 (27.78%) | | |
| occurrences (all) | 8 | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Dysuria | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |

| | | | |
|---|-----------------|--|--|
| Pollakiuria | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 2 | | |
| Renal impairment | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences (all) | 0 | | |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences (all) | 2 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 6 / 18 (33.33%) | | |
| occurrences (all) | 12 | | |
| Back pain | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences (all) | 2 | | |
| Myalgia | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences (all) | 3 | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences (all) | 0 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 3 / 18 (16.67%) | | |
| occurrences (all) | 4 | | |
| Muscular weakness | | | |
| subjects affected / exposed | 3 / 18 (16.67%) | | |
| occurrences (all) | 4 | | |
| Flank pain | | | |

| | | | |
|-----------------------------------|-----------------|--|--|
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences (all) | 2 | | |
| Bone pain | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Infections and infestations | | | |
| Paronychia | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences (all) | 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| occurrences (all) | 0 | | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Fungal infection | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Herpes virus infection | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Rash pustular | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |

| | | | |
|---|----------------------|--|--|
| Respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 2 / 18 (11.11%) 2 | | |
| Hypokalaemia subjects affected / exposed occurrences (all) | 2 / 18 (11.11%) 2 | | |
| Hypomagnesaemia subjects affected / exposed occurrences (all) | 2 / 18 (11.11%) 3 | | |
| Dehydration subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | | |
| Hypocalcaemia subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | | |
| Hypophosphataemia subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 2 | | |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | | |
| Hyperuricaemia subjects affected / exposed occurrences (all) | 2 / 18 (11.11%) 2 | | |
| Gout subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | | |
| Hyponatraemia subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 16 February 2016 | <ul style="list-style-type: none">• New starting dose of 560 mg for ibrutinib• Dose escalation clinical trial design for Phase 1b• Revised inclusion criteria for CRC cohort• Revised eligibility criteria for subjects with platelet counts above $100 \times 10^9/L$ to match relevant labelling• Revise eligibility criteria for hemoglobin• Revised DLT criteria• Refined DLT evaluable population• Updated Pharmacodynamics Collection Schedule• Updated protocol template language to align with most current Investigator's Brochure |
| 25 January 2019 | <ul style="list-style-type: none">• Cohort 5 (single agent ibrutinib) was added to the study• Summary of Clinical Safety section was updated to align with the current ibrutinib Investigator's Brochure (version 12.0)• Summary of Clinical Data section was updated to provide safety data from the interim analysis of Study 1128• Rationale in Specific Solid Tumors section was updated to include information on UC and GC solid tumors• Dosing Rationale section was updated to include the rationale for the 560 mg and 840 mg starting doses (for UC and Cohorts 2 and 5)• The study objectives were updated to include the primary objectives in Phase 1b and Phase 2 and the secondary objectives in Phase 2 for Cohort 5• Background information on safety and efficacy of ibrutinib monotherapy in previously treated UC and combination therapy in previously treated UC and GC was added to the Overview of Study Design• Updates were made to the permitted concomitant medications• Updates were made to minor surgical procedures to include information pertinent to UC Cohort 5 |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported