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	• New data added to full data set Completion 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 × 2.5 mg tablets or 2 × 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/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.

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 Paxlitaxel 80 mg/m^2 IV (4 patients) followed by Ibrutinib 840 mg and the same dose of Paxlitaxel (10 patients). In Phase 2, 57 additional patients were treated with Ibrutinib 840 mg PO qd and Paxlitaxel 80 mg/m^2 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/m^2 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/m^2 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/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.

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 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

No statistical analyses for this end point

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	0 / 135 (0.00%)	3 / 59 (5.08%)	0 / 35 (0.00%)
occurrences (all)	0	3	0
Investigations			
Weight decreased			
subjects affected / exposed	17 / 135 (12.59%)	0 / 59 (0.00%)	3 / 35 (8.57%)
occurrences (all)	21	0	4
Platelet count decreased			
subjects affected / exposed	14 / 135 (10.37%)	7 / 59 (11.86%)	0 / 35 (0.00%)
occurrences (all)	19	11	0
Aspartate aminotransferase increased			
subjects affected / exposed	11 / 135 (8.15%)	4 / 59 (6.78%)	0 / 35 (0.00%)
occurrences (all)	12	10	0
Neutrophil count decreased			
subjects affected / exposed	11 / 135 (8.15%)	9 / 59 (15.25%)	0 / 35 (0.00%)
occurrences (all)	24	11	0
Blood creatinine increased			
subjects affected / exposed	10 / 135 (7.41%)	0 / 59 (0.00%)	0 / 35 (0.00%)
occurrences (all)	24	0	0
White blood cell count decreased			
subjects affected / exposed	9 / 135 (6.67%)	0 / 59 (0.00%)	0 / 35 (0.00%)
occurrences (all)	18	0	0
Alanine aminotransferase increased			
subjects affected / exposed	8 / 135 (5.93%)	4 / 59 (6.78%)	0 / 35 (0.00%)
occurrences (all)	9	15	0
Protein urine present			
subjects affected / exposed	0 / 135 (0.00%)	0 / 59 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			
subjects affected / exposed	0 / 135 (0.00%)	0 / 59 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 135 (0.00%)	0 / 59 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	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	0 / 135 (0.00%)	0 / 59 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Oral mucosal erythema			
subjects affected / exposed	0 / 135 (0.00%)	0 / 59 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Abdominal distension			
subjects affected / exposed	0 / 135 (0.00%)	0 / 59 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	2
Haemorrhoids			
subjects affected / exposed	0 / 135 (0.00%)	3 / 59 (5.08%)	0 / 35 (0.00%)
occurrences (all)	0	3	0
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 135 (0.00%)	0 / 59 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Hepatic function abnormal			
subjects affected / exposed	0 / 135 (0.00%)	0 / 59 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	4
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	48 / 135 (35.56%)	7 / 59 (11.86%)	0 / 35 (0.00%)
occurrences (all)	160	11	0
Pruritus			
subjects affected / exposed	30 / 135 (22.22%)	4 / 59 (6.78%)	3 / 35 (8.57%)
occurrences (all)	42	5	3
Dry skin			
subjects affected / exposed	27 / 135 (20.00%)	7 / 59 (11.86%)	2 / 35 (5.71%)
occurrences (all)	45	9	2
Rash maculo-papular			
subjects affected / exposed	19 / 135 (14.07%)	5 / 59 (8.47%)	2 / 35 (5.71%)
occurrences (all)	71	11	2
Alopecia			
subjects affected / exposed	17 / 135 (12.59%)	18 / 59 (30.51%)	0 / 35 (0.00%)
occurrences (all)	20	24	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	0 / 135 (0.00%)	0 / 59 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 135 (0.00%)	3 / 59 (5.08%)	0 / 35 (0.00%)
occurrences (all)	0	3	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	50 / 135 (37.04%)	25 / 59 (42.37%)	12 / 35 (34.29%)
occurrences (all)	92	50	15
Hypokalaemia			
subjects affected / exposed	18 / 135 (13.33%)	7 / 59 (11.86%)	0 / 35 (0.00%)
occurrences (all)	33	9	0
Hypomagnesaemia			
subjects affected / exposed	16 / 135 (11.85%)	6 / 59 (10.17%)	3 / 35 (8.57%)
occurrences (all)	35	10	4
Dehydration			
subjects affected / exposed	8 / 135 (5.93%)	0 / 59 (0.00%)	0 / 35 (0.00%)
occurrences (all)	9	0	0
Hypocalcaemia			
subjects affected / exposed	8 / 135 (5.93%)	0 / 59 (0.00%)	0 / 35 (0.00%)
occurrences (all)	14	0	0
Hypophosphataemia			
subjects affected / exposed	8 / 135 (5.93%)	0 / 59 (0.00%)	0 / 35 (0.00%)
occurrences (all)	12	0	0
Hyperglycaemia			
subjects affected / exposed	7 / 135 (5.19%)	0 / 59 (0.00%)	0 / 35 (0.00%)
occurrences (all)	21	0	0
Hyperuricaemia			
subjects affected / exposed	0 / 135 (0.00%)	0 / 59 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Gout			
subjects affected / exposed	0 / 135 (0.00%)	0 / 59 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	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) Non-cardiac chest pain subjects affected / exposed occurrences (all) Swelling subjects affected / exposed occurrences (all) Gait disturbance subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1 1 / 18 (5.56%) 1 1 / 18 (5.56%) 1 0 / 18 (0.00%) 0		
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1 1 / 18 (5.56%) 1		
Reproductive system and breast disorders Vaginal discharge subjects affected / exposed occurrences (all) Balanoposthitis subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 2 0 / 18 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2 0 / 18 (0.00%) 0 0 / 18 (0.00%) 0		

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

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

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	• 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 × 109/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	• 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