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	

Results information

Result version number	v1
This version publication date	10 February 2021
First version publication date	10 February 2021

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
Sponsor organisation address	999 East Arques Ave, Sunnyvale, CA, United States, 94085
Public contact	Clinical Trial information, Pharmacyclics LLC, Pharmacyclics LLC, 1 4087740330, info@pcyc.com
Scientific contact	Clinical Trial information, Pharmacyclics LLC , Pharmacyclics LLC, 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	Interim
Date of interim/final analysis	23 March 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 January 2020
Global end of trial reached?	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 RCC, paclitaxel in urothelial carcinoma, docetaxel in gastric adenocarcinoma and cetuximab in CRC.

Phase 2:
Primary Objectives:
- To assess progression-free survival (PFS) of ibrutinib combination therapy in RCC and urothelial carcinoma
- To assess the ORR of ibrutinib combination therapy in gastric adenocarcinoma and CRC

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	17 November 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	Spain: 32
Country: Number of subjects enrolled	United Kingdom: 25
Country: Number of subjects enrolled	Korea, Republic of: 48
Country: Number of subjects enrolled	United States: 41
Worldwide total number of subjects	146
EEA total number of subjects	57

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	88
From 65 to 84 years	58
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 38 sites: 18 in the US, 8 in the South Korea, 4 in the UK and 8 in Spain. The first subject consented 01 Dec 2015 and the last visit of the last subjects for this interim analysis was 27 Jan 2020.

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. 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.

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, non-fatal	13	8	9
Death	-	-	1

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 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
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	Total		
Number of subjects	146		
Age categorical Units: Subjects			
Adults (18-64 years)	88		
From 65-84 years	58		
Age continuous Units: years			
median			
full range (min-max)	-		

Gender categorical Units: Subjects			
Female	49		
Male	97		

Subject analysis sets

Subject analysis set title	Analysis set 1: Phase 1 RCC subjects not treated with RP2D
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Covering subjects in the Phase 1 RCC cohort treated with 560 mg ibrutinib instead of 840 mg ibrutinib (RP2D) in combination with everolimus.

Subject analysis set title	Analysis Set 2: Phase 1 CRC subjects not treated with RP2D
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Covering subjects in the Phase 1 CRC cohort treated with 560 mg ibrutinib instead of 840 mg ibrutinib (RP2D) in combination with cetuximab.

Subject analysis set title	Analysis Set 3: All RCC subjects treated with RP2D
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All RCC subjects in Phase 1 and Phase 2 treated with the RP2D of 840 mg ibrutinib.

Subject analysis set title	Analysis Set 4: All GC subjects treated with RP2D
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All GC subjects in Phase 1 and Phase 2 treated with the RP2D of 560 mg ibrutinib.

Subject analysis set title	Analysis Set 5: All CRC subjects treated with RP2D
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All CRC subjects in Phase 1 and Phase 2 treated with the RP2D of 840 mg ibrutinib.

Reporting group values	Analysis set 1: Phase 1 RCC subjects not treated with RP2D	Analysis Set 2: Phase 1 CRC subjects not treated with RP2D	Analysis Set 3: All RCC subjects treated with RP2D
Number of subjects	3	8	39
Age categorical Units: Subjects			
Adults (18-64 years)	1	6	23
From 65-84 years	2	2	16
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	Analysis Set 4: All GC subjects treated with RP2D	Analysis Set 5: All CRC subjects treated with RP2D	
Number of subjects	46	50	

Age categorical Units: Subjects			
Adults (18-64 years)	33	25	
From 65-84 years	13	25	
Age continuous Units: years			
median	58	64	
full range (min-max)	35 to 77	32 to 81	
Gender categorical Units: Subjects			
Female	12	21	
Male	34	29	

End points

End points reporting groups

Reporting group title	Renal cell carcinoma

Reporting group description:

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

Reporting group title	Gastric Adenocarcinoma

Reporting group description:

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

Reporting group title	Colorectal Adenocarcinoma

Reporting group description:

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

Subject analysis set title	Analysis set 1: Phase 1 RCC subjects not treated with RP2D
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Covering subjects in the Phase 1 RCC cohort treated with 560 mg ibrutinib instead of 840 mg ibrutinib (RP2D) in combination with everolimus.

Subject analysis set title	Analysis Set 2: Phase 1 CRC subjects not treated with RP2D
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Covering subjects in the Phase 1 CRC cohort treated with 560 mg ibrutinib instead of 840 mg ibrutinib (RP2D) in combination with cetuximab.

Subject analysis set title	Analysis Set 3: All RCC subjects treated with RP2D
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All RCC subjects in Phase 1 and Phase 2 treated with the RP2D of 840 mg ibrutinib.

Subject analysis set title	Analysis Set 4: All GC subjects treated with RP2D
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All GC subjects in Phase 1 and Phase 2 treated with the RP2D of 560 mg ibrutinib.

Subject analysis set title	Analysis Set 5: All CRC subjects treated with RP2D
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All CRC subjects in Phase 1 and Phase 2 treated with the RP2D of 840 mg ibrutinib.

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 in the RCC arm and secondary endpoint in the GC and CRC arms. The evaluations are based on the efficacy evaluable population treated with the RP2D.

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 (Phase 1 incl. RP2D dose/Phase 2), in the GC arm of 25.3 /11.1 mo (Phase 1/Phase 2), and in the CRC arm of 34.1/22.1 mo (Phase 1 incl. PR2D dose/Phase 2)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As this is a Phase 1/2 open label study with 6 different cohorts covering different indications, no comparisons were applicable and therefore no statistical analyses have been performed.

End point values	Analysis Set 3: All RCC subjects treated with RP2D	Analysis Set 4: All GC subjects treated with RP2D	Analysis Set 5: All CRC subjects treated with RP2D	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	36[2]	39[3]	47[4]	
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)	

Notes:

[2] - Efficacy Evaluable Population

[3] - Efficacy Evaluable Population

[4] - Efficacy Evaluable Population

Statistical analyses

No statistical analyses for this end point

Primary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)[5]

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 and CRC arms and secondary endpoint in the RCC arm. The evaluations are based on the efficacy evaluable population treated with the RP2D.

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 (Phase 1 incl. RP2D dose/Phase 2), in the GC arm of 25.3 /11.1 mo (Phase 1/Phase 2), and in the CRC arm of 34.1/22.1 mo (Phase 1 incl. PR2D dose/Phase 2)

Notes:

[5] - 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: As this is a Phase 1/2 open label study with 6 different cohorts covering different indications, no comparisons were applicable and therefore no statistical analyses have been performed.

End point values	Analysis Set 3: All RCC subjects treated with RP2D	Analysis Set 4: All GC subjects treated with RP2D	Analysis Set 5: All CRC subjects treated with RP2D	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	36[6]	39[7]	47[8]	
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)	

Notes:

[6] - Efficacy Evaluable Population

[7] - Efficacy Evaluable Population

[8] - 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.

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

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 (Phase 1 incl. RP2D dose/Phase 2), in the GC arm of 25.3 /11.1 mo (Phase 1/Phase 2), and in the CRC arm of 34.1/22.1 mo (Phase 1 incl. PR2D dose/Phase 2)

End point values	Analysis Set 3: All RCC subjects treated with RP2D	Analysis Set 4: All GC subjects treated with RP2D	Analysis Set 5: All CRC subjects treated with RP2D	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	36[9]	39[10]	47[11]	
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)	

Notes:

[9] - Efficacy Evaluable Population

[10] - Efficacy Evaluable Population

[11] - 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.

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 (Phase 1 incl. RP2D dose/Phase 2), in the GC arm of 25.3 /11.1 mo (Phase 1/Phase 2), and in the CRC arm of 34.1/22.1 mo (Phase 1 incl. PR2D dose/Phase 2)

End point values	Analysis Set 3: All RCC subjects treated with RP2D	Analysis Set 4: All GC subjects treated with RP2D	Analysis Set 5: All CRC subjects treated with RP2D	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	36[12]	39[13]	47[14]	
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)	

Notes:

[12] - Efficacy Evaluable Population

[13] - Efficacy Evaluable Population

[14] - 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.

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 (Phase 1 incl. RP2D dose/Phase 2), in the GC arm of 25.3 /11.1 mo (Phase 1/Phase 2), and in the CRC arm of 34.1/22.1 mo (Phase 1 incl. PR2D dose/Phase 2)

End point values	Analysis Set 3: All RCC subjects treated with RP2D	Analysis Set 4: All GC subjects treated with RP2D	Analysis Set 5: All CRC subjects treated with RP2D	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	1	7	7	
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)	

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.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Subjects treated with RP2D

Reporting group description:

Safety is reported here for all subjects treated with the RP2D regardless of the indication. Safety of subjects treated with lower doses in the Phase I part of the study are not reported due to the low number of subjects,

Serious adverse events	Subjects treated with RP2D		
Total subjects affected by serious adverse events			
subjects affected / exposed	62 / 135 (45.93%)		
number of deaths (all causes)	88		
number of deaths resulting from adverse events	7		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Colorectal adenocarcinoma			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric cancer			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to central nervous system			

subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to spine			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal cell carcinoma			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Tumour haemorrhage			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Aortic stenosis			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Pleurodesis			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 135 (2.96%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 0		

Generalised oedema				
subjects affected / exposed	2 / 135 (1.48%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Multiple organ dysfunction syndrome				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Dyspnoea				
subjects affected / exposed	3 / 135 (2.22%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	2 / 135 (1.48%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			

Pneumonia aspiration				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Respiratory failure				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Gun shot wound				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiac disorders				
Atrial fibrillation				
subjects affected / exposed	2 / 135 (1.48%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Bradycardia				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Myocardial infarction				
subjects affected / exposed	1 / 135 (0.74%)			
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	2 / 135 (1.48%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cerebral haemorrhage				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral infarction				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral ischaemia				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Presyncope				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Radiculopathy				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				

Febrile neutropenia				
subjects affected / exposed	11 / 135 (8.15%)			
occurrences causally related to treatment / all	8 / 14			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	4 / 135 (2.96%)			
occurrences causally related to treatment / all	3 / 6			
deaths causally related to treatment / all	0 / 0			
Anaemia				
subjects affected / exposed	3 / 135 (2.22%)			
occurrences causally related to treatment / all	4 / 5			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	4 / 135 (2.96%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	3 / 135 (2.22%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	3 / 135 (2.22%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Stomatitis				
subjects affected / exposed	3 / 135 (2.22%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	2 / 135 (1.48%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				

subjects affected / exposed	2 / 135 (1.48%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Melaena				
subjects affected / exposed	2 / 135 (1.48%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal motility disorder				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haematemesis				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Nausea				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Obstruction gastric				

subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Renal Failure			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neck mass			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Infections and infestations			
Pneumonia			
subjects affected / exposed	8 / 135 (5.93%)		
occurrences causally related to treatment / all	1 / 9		
deaths causally related to treatment / all	0 / 0		
Neutropenic sepsis			
subjects affected / exposed	5 / 135 (3.70%)		
occurrences causally related to treatment / all	4 / 5		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Atypical pneumonia			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Biliary tract infection			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Clostridium difficile infection			

subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enterococcal bacteraemia			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes simplex			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Meningitis aseptic			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Paronychia			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcal infection			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dehydration			

subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetic ketoacidosis			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperphosphataemia			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 3		
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		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	132 / 135 (97.78%)		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	52 / 135 (38.52%)		
occurrences (all)	120		
Asthenia			
subjects affected / exposed	35 / 135 (25.93%)		
occurrences (all)	91		
Oedema peripheral			
subjects affected / exposed	21 / 135 (15.56%)		
occurrences (all)	29		
Pyrexia			
subjects affected / exposed	21 / 135 (15.56%)		
occurrences (all)	27		

Chills			
subjects affected / exposed	7 / 135 (5.19%)		
occurrences (all)	10		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	37 / 135 (27.41%)		
occurrences (all)	54		
Cough			
subjects affected / exposed	24 / 135 (17.78%)		
occurrences (all)	37		
Dyspnoea			
subjects affected / exposed	12 / 135 (8.89%)		
occurrences (all)	25		
Oropharyngeal pain			
subjects affected / exposed	11 / 135 (8.15%)		
occurrences (all)	13		
Haemoptysis			
subjects affected / exposed	8 / 135 (5.93%)		
occurrences (all)	10		
Productive cough			
subjects affected / exposed	8 / 135 (5.93%)		
occurrences (all)	10		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	11 / 135 (8.15%)		
occurrences (all)	14		
Investigations			
Weight decreased			
subjects affected / exposed	17 / 135 (12.59%)		
occurrences (all)	21		
Platelet count decreased			
subjects affected / exposed	14 / 135 (10.37%)		
occurrences (all)	19		
Aspartate aminotransferase increased			
subjects affected / exposed	11 / 135 (8.15%)		
occurrences (all)	12		

Neutrophil count decreased subjects affected / exposed occurrences (all)	11 / 135 (8.15%) 24		
Blood creatinine increased subjects affected / exposed occurrences (all)	10 / 135 (7.41%) 24		
White blood cell count decreased subjects affected / exposed occurrences (all)	9 / 135 (6.67%) 18		
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	8 / 135 (5.93%) 9		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	22 / 135 (16.30%) 28		
Headache subjects affected / exposed occurrences (all)	12 / 135 (8.89%) 16		
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	11 / 135 (8.15%) 16		
Neurotoxicity subjects affected / exposed occurrences (all)	7 / 135 (5.19%) 21		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	51 / 135 (37.78%) 160		
Thrombocytopenia subjects affected / exposed occurrences (all)	24 / 135 (17.78%) 55		
Neutropenia subjects affected / exposed occurrences (all)	18 / 135 (13.33%) 46		
Eye disorders			

Dry eye subjects affected / exposed occurrences (all)	7 / 135 (5.19%) 10		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	70 / 135 (51.85%) 148		
Stomatitis subjects affected / exposed occurrences (all)	68 / 135 (50.37%) 154		
Nausea subjects affected / exposed occurrences (all)	46 / 135 (34.07%) 82		
Vomiting subjects affected / exposed occurrences (all)	34 / 135 (25.19%) 55		
Constipation subjects affected / exposed occurrences (all)	23 / 135 (17.04%) 26		
Abdominal pain subjects affected / exposed occurrences (all)	18 / 135 (13.33%) 27		
Dyspepsia subjects affected / exposed occurrences (all)	17 / 135 (12.59%) 20		
Abdominal pain upper subjects affected / exposed occurrences (all)	13 / 135 (9.63%) 19		
Dry mouth subjects affected / exposed occurrences (all)	10 / 135 (7.41%) 22		
Dysphagia subjects affected / exposed occurrences (all)	7 / 135 (5.19%) 9		
Skin and subcutaneous tissue disorders			

Dermatitis acneiform subjects affected / exposed occurrences (all)	48 / 135 (35.56%) 160		
Pruritus subjects affected / exposed occurrences (all)	30 / 135 (22.22%) 42		
Dry skin subjects affected / exposed occurrences (all)	27 / 135 (20.00%) 45		
Rash maculo-papular subjects affected / exposed occurrences (all)	19 / 135 (14.07%) 71		
Alopecia subjects affected / exposed occurrences (all)	17 / 135 (12.59%) 20		
Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all)	16 / 135 (11.85%) 38		
Petechiae subjects affected / exposed occurrences (all)	9 / 135 (6.67%) 17		
Rash erythematous subjects affected / exposed occurrences (all)	9 / 135 (6.67%) 12		
Rash subjects affected / exposed occurrences (all)	8 / 135 (5.93%) 10		
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	9 / 135 (6.67%) 18		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	16 / 135 (11.85%) 27		
Back pain			

subjects affected / exposed	13 / 135 (9.63%)		
occurrences (all)	14		
Myalgia			
subjects affected / exposed	12 / 135 (8.89%)		
occurrences (all)	16		
Pain in extremity			
subjects affected / exposed	9 / 135 (6.67%)		
occurrences (all)	14		
Musculoskeletal pain			
subjects affected / exposed	7 / 135 (5.19%)		
occurrences (all)	8		
Infections and infestations			
Paronychia			
subjects affected / exposed	29 / 135 (21.48%)		
occurrences (all)	54		
Urinary tract infection			
subjects affected / exposed	11 / 135 (8.15%)		
occurrences (all)	13		
Conjunctivitis			
subjects affected / exposed	9 / 135 (6.67%)		
occurrences (all)	13		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	50 / 135 (37.04%)		
occurrences (all)	92		
Hypokalaemia			
subjects affected / exposed	18 / 135 (13.33%)		
occurrences (all)	33		
Hypomagnesaemia			
subjects affected / exposed	16 / 135 (11.85%)		
occurrences (all)	35		
Dehydration			
subjects affected / exposed	8 / 135 (5.93%)		
occurrences (all)	9		
Hypocalcaemia			

subjects affected / exposed	8 / 135 (5.93%)		
occurrences (all)	14		
Hypophosphataemia			
subjects affected / exposed	8 / 135 (5.93%)		
occurrences (all)	12		
Hyperglycaemia			
subjects affected / exposed	7 / 135 (5.19%)		
occurrences (all)	21		

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