



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 x 2.5 mg tablets or 2 x 5.0 mg tablets could be substituted if 10 mg tablets were not available. Everolimus tablets were to be taken approximately 6 hours after ibrutinib capsules.

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

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

Arm description:

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

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

Dosage and administration details:

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

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

Dosage and administration details:

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

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

Arm description:

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

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

Dosage and administration details:

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

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

Dosage and administration details:

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

| 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. RP2D 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. RP2D 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. RP2D 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 occurrences causally related to treatment / all deaths causally related to treatment / all | 8 / 135 (5.93%) 1 / 9 0 / 0 | | |
| Neutropenic sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 5 / 135 (3.70%) 4 / 5 0 / 0 | | |
| Respiratory tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 2 / 135 (1.48%) 0 / 2 0 / 0 | | |
| Sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 2 / 135 (1.48%) 0 / 2 0 / 0 | | |
| Upper respiratory tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 2 / 135 (1.48%) 0 / 2 0 / 0 | | |
| Appendicitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 135 (0.74%) 1 / 1 0 / 0 | | |
| Atypical pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 135 (0.74%) 0 / 1 0 / 0 | | |
| Biliary tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 135 (0.74%) 0 / 1 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 occurrences (all) | 7 / 135 (5.19%) 10 | | |
| Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Haemoptysis subjects affected / exposed occurrences (all) Productive cough subjects affected / exposed occurrences (all) | 37 / 135 (27.41%) 54 24 / 135 (17.78%) 37 12 / 135 (8.89%) 25 11 / 135 (8.15%) 13 8 / 135 (5.93%) 10 8 / 135 (5.93%) 10 | | |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 11 / 135 (8.15%) 14 | | |
| Investigations Weight decreased subjects affected / exposed occurrences (all) Platelet count decreased subjects affected / exposed occurrences (all) Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 17 / 135 (12.59%) 21 14 / 135 (10.37%) 19 11 / 135 (8.15%) 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 erythrodysesthesia 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 | <ul style="list-style-type: none">• New starting dose of 560 mg for ibrutinib• Dose escalation clinical trial design for Phase 1b• Revised inclusion criteria for CRC cohort• Revised eligibility criteria for subjects with platelet counts above $100 \times 10^9/L$ to match relevant labelling• Revise eligibility criteria for hemoglobin• Revised DLT criteria• Refined DLT evaluable population• Updated Pharmacodynamics Collection Schedule• Updated protocol template language to align with most current Investigator's Brochure |
| 25 January 2019 | <ul style="list-style-type: none">• Cohort 5 (single agent ibrutinib) was added to the study• Summary of Clinical Safety section was updated to align with the current ibrutinib Investigator's Brochure (version 12.0)• Summary of Clinical Data section was updated to provide safety data from the interim analysis of Study 1128• Rationale in Specific Solid Tumors section was updated to include information on UC and GC solid tumors• Dosing Rationale section was updated to include the rationale for the 560 mg and 840 mg starting doses (for UC and Cohorts 2 and 5)• The study objectives were updated to include the primary objectives in Phase 1b and Phase 2 and the secondary objectives in Phase 2 for Cohort 5• Background information on safety and efficacy of ibrutinib monotherapy in previously treated UC and combination therapy in previously treated UC and GC was added to the Overview of Study Design• Updates were made to the permitted concomitant medications• Updates were made to minor surgical procedures to include information pertinent to UC Cohort 5 |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported