



Clinical trial results:

A Phase IIa Exploratory Study of CriPec® docetaxel Monotherapy in Subjects with Platinum Resistant Ovarian Cancer.

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2018-002117-36 |
| Trial protocol | NL BE GB |
| Global end of trial date | 06 July 2020 |

Results information

| | |
|-----------------------------------|---|
| Result version number | v1 (current) |
| This version publication date | 08 January 2021 |
| First version publication date | 08 January 2021 |
| Summary attachment (see zip file) | SMS-0423_CINOVA_Synopsis final CSR_01Dec2020_signed (SMS-0423_CINOVA_Synopsis final CSR_01Dec2020_signed.pdf) |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | CT-CL02 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------------------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03742713 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | SMS-oncology study number: SMS-0423 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Cristal Therapeutics |
| Sponsor organisation address | Oxfordlaan 55, Maastricht, Netherlands, 6229 EV |
| Public contact | Rob Hanssen, Cristal Therapeutics, info@cristaltherapeutics.com |
| Scientific contact | Rob Hanssen, Cristal Therapeutics, info@cristaltherapeutics.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 01 October 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 06 July 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 06 July 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To determine the Objective Response Rate (ORR) as assessed by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 of CriPec® docetaxel monotherapy in subjects with ovarian cancer who are resistant to prior platinum-based therapy.

Protection of trial subjects:

Corticosteroid pre-medication was administered to prevent skin toxicities.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 19 October 2018 |
| 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 | Netherlands: 10 |
| Country: Number of subjects enrolled | Belgium: 15 |
| Worldwide total number of subjects | 25 |
| EEA total number of subjects | 25 |

Notes:

Subjects enrolled per age group

| | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 11 |
| From 65 to 84 years | 14 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This trial was conducted in 8 centers divided over 3 countries: The Netherlands, Belgium and the United Kingdom. 6 out of 8 centers recruited patients. First patient was included 19Oct2018. Last study visit before database lock was 06Jul2020.

Pre-assignment

Screening details:

Patients with ovarian and peritoneal cancer resistant to prior platinum-based therapy. Total number of patients was 25 with 25 being part of the safety set population, and 23 being part of the per protocol set.

Stage 1: first 13 patients included

Stage 2: altered inclusion criteria to match those of hallmark Docetaxel trials

Period 1

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

Arms

| | |
|-----------|---|
| Arm title | Received at least one dose CriPec©docetaxel |
|-----------|---|

Arm description:

Subjects eligible for the trial received CriPec®docetaxel Q3W at the RP2D of 60 mg/m². Each treatment cycle consisted of 21 days. On Day 1 of each cycle, a single dose of CriPec®docetaxel was administered IV at a constant rate for ~1 hour. Pre-treatment with dexamethasone 8.0 mg orally was given three times before each CriPec®docetaxel administration (night before, morning and 1 hour before treatment).

Stage 1: (N=13) Simon 2-stage design.

Stage 2: (N=12). Simon 2-stage design no longer applicable. Maximum allowed treatment lines reduced from 3 to 2 lines, in both cases of which one could have been taxane-based. Life expectancy requirement extended from 12 weeks to 5 months.

| | |
|--|----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | CriPec©docetaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

The dose selection for CT-CL02 was based on previous experience from trial CT-CL01, where the R2PD of 60 mg/m² with corticosteroid premedication was selected based on the following:

- There was a significant decrease of skin toxicities (all severity grades) comparing 70 mg/m² to 60 mg/m² dose level at the Q3W schedule;
- Addition of corticosteroid premedication to the 60 mg/m²/Q3W regimen prevented acute skin reactions. Also, at the 60 mg/m² dose plus corticosteroids, overall less AEs have been reported;
- The average length of therapy at 60 mg/m² plus corticosteroids was longer (~5.2 treatment cycles) than without co-medication (~3.2 treatment cycles);

The complete dose of CriPec®docetaxel had to be administered via IV infusion. Start and stop times had to be noted. If the administration was interrupted and subsequently restarted, the start and stop times of the re-administration must have also been noted.

| Number of subjects in period 1 | Received at least one dose CriPec@docetaxel |
|---------------------------------------|---|
| Started | 25 |
| Completed | 25 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Overall trial |
|-----------------------|---------------|

Reporting group description:

Q3W IV CriPec®docetaxel administration at 60mg/m², with corticosteroid premedication (three times 8.0 mg oral dexamethasone before each CriPec®docetaxel dose).

* Stage 1 (N=13): There was no limit to the number of previous treatment lines, but a maximum of 3 lines of therapy for platinum-resistant disease, of which one could have been taxane-based. Life expectancy required of at least 12 weeks.

* Stage 2: Subjects who have received a maximum of 2 prior treatment lines, of which one could have been taxane-based. Life expectancy required of at least 5 months.

| Reporting group values | Overall trial | Total | |
|--|---------------|-------|--|
| Number of subjects | 25 | 25 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 11 | 11 | |
| From 65-84 years | 14 | 14 | |
| 85 years and over | 0 | 0 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 25 | 25 | |
| Male | 0 | 0 | |
| Number of previous treatment lines | | | |
| PD was recorded in all subjects who had previously received four or five lines of therapy (four lines: three subjects in Stage 1 and one subject in Stage 2; five lines: three subjects in Stage 1). Previous treatment lines include: Platinum compounds, Taxanes, Anthracyclines and related, Monoclonal antibodies, Other antineoplastic agents, Pyrimidine analogues, Aromatase inhibitors, Investigational drugs and Antineoplastic agents. | | | |
| Units: Subjects | | | |
| 1 treatment line | 1 | 1 | |
| 2 treatment lines | 9 | 9 | |
| 3 treatment lines | 8 | 8 | |
| 4 treatment lines | 4 | 4 | |
| 5 treatment lines | 3 | 3 | |

Subject analysis sets

| | |
|----------------------------|--------------------|
| Subject analysis set title | Stage 1 |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

There was no limit to the number of previous treatment lines, but a maximum of 3 lines of therapy for platinum-resistant disease, of which one could have been taxane-based. Life expectancy required of at least 12 weeks.

| | |
|----------------------------|--------------------|
| Subject analysis set title | Stage 2 |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Subjects who have received a maximum of 2 prior treatment lines, of which one could have been taxane-based. Life expectancy required of at least 5 months.

| Reporting group values | Stage 1 | Stage 2 | |
|--|---------|---------|--|
| Number of subjects | 13 | 12 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 9 | 2 | |
| From 65-84 years | 4 | 10 | |
| 85 years and over | 0 | 0 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 13 | 12 | |
| Male | 0 | 0 | |
| Number of previous treatment lines | | | |
| PD was recorded in all subjects who had previously received four or five lines of therapy (four lines: three subjects in Stage 1 and one subject in Stage 2; five lines: three subjects in Stage 1). Previous treatment lines include: Platinum compounds, Taxanes, Anthracyclines and related, Monoclonal antibodies, Other antineoplastic agents, Pyrimidine analogues, Aromatase inhibitors, Investigational drugs and Antineoplastic agents. | | | |
| Units: Subjects | | | |
| 1 treatment line | 0 | 1 | |
| 2 treatment lines | 0 | 9 | |
| 3 treatment lines | 7 | 1 | |
| 4 treatment lines | 3 | 1 | |
| 5 treatment lines | 3 | 0 | |

End points

End points reporting groups

| | |
|-----------------------|---|
| Reporting group title | Received at least one dose CriPec@docetaxel |
|-----------------------|---|

Reporting group description:

Subjects eligible for the trial received CriPec@docetaxel Q3W at the RP2D of 60 mg/m². Each treatment cycle consisted of 21 days. On Day 1 of each cycle, a single dose of CriPec@docetaxel was administered IV at a constant rate for ~1 hour. Pre-treatment with dexamethasone 8.0 mg orally was given three times before each CriPec@docetaxel administration (night before, morning and 1 hour before treatment).

Stage 1: (N=13) Simon 2-stage design.

Stage 2: (N=12). Simon 2-stage design no longer applicable. Maximum allowed treatment lines reduced from 3 to 2 lines, in both cases of which one could have been taxane-based. Life expectancy requirement extended from 12 weeks to 5 months.

| | |
|----------------------------|--------------------|
| Subject analysis set title | Stage 1 |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

There was no limit to the number of previous treatment lines, but a maximum of 3 lines of therapy for platinum-resistant disease, of which one could have been taxane-based. Life expectancy required of at least 12 weeks.

| | |
|----------------------------|--------------------|
| Subject analysis set title | Stage 2 |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Subjects who have received a maximum of 2 prior treatment lines, of which one could have been taxane-based. Life expectancy required of at least 5 months.

Primary: ORR as assessed by RECISTV1.1 calculated as proportion of subjects who achieved CR or PR

| | |
|-----------------|---|
| End point title | ORR as assessed by RECISTV1.1 calculated as proportion of subjects who achieved CR or PR ^[1] |
|-----------------|---|

End point description:

ORR as assessed by RECISTV1.1

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

End point timeframe:

At any time point prior to end of trial (when the subject had either discontinued trial treatment or received six cycles of treatment, whichever occurred first).

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: The analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed.

| End point values | Received at least one dose CriPec@docetaxel | Stage 1 | Stage 2 | |
|------------------------------|---|----------------------|----------------------|--|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 20 | 13 | 7 | |
| Units: Best overall response | | | | |
| CR | 0 | 0 | 0 | |
| PR | 0 | 0 | 0 | |
| SD | 7 | 3 | 4 | |
| PD | 13 | 10 | 3 | |
| Objective response rate | 0 | 0 | 0 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Safety, evaluated by means of physical examinations, body weight, vital signs, ECOG, lab, ECG and AEs

| | |
|-----------------|---|
| End point title | Safety, evaluated by means of physical examinations, body weight, vital signs, ECOG, lab, ECG and AEs |
|-----------------|---|

End point description:

For physical examinations, body weight, vital signs lab, and ECG parameters no clear impact on safety could be detected. For an overview of the Adverse Events, please refer to the Adverse Event section of this report.

ECOG changes during the trial to higher grades were generally recorded for higher numbers of subjects in Stage 2 than in Stage 1.

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

End point timeframe:

Safety parameters were recorded from screening until day 22 of the last cycle (EOT). Both ECOG and vital signs were additionally recorded at the safety follow-up visit 28 days after EOT. SAEs regarded related to IMP were followed until end of study.

| End point values | Received at least one dose CriPec@docetaxel | Stage 1 | Stage 2 | |
|--|---|----------------------|----------------------|--|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 25 | 13 | 12 | |
| Units: ECOG worsening | | | | |
| Baseline ECOG 0 - No worsening | 6 | 6 | 0 | |
| Baseline ECOG 0 - Worsening to ECOG 1 | 6 | 2 | 4 | |
| Baseline ECOG 0 - Worsening to ECOG 2 | 2 | 1 | 1 | |
| Baseline ECOG 0 - Worsening to ECOG 3 | 1 | 0 | 1 | |
| Baseline ECOG 1 - No worsening | 5 | 3 | 2 | |
| Baseline ECOG 1 - Worsening to ECOG 2 | 2 | 0 | 2 | |
| Baseline ECOG 1 - Worsening to ECOG 3 | 2 | 1 | 1 | |
| No post-baseline ECOG assessment performed | 1 | 0 | 1 | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Subjects were monitored for AEs from screening and during each subject visit until 22 days after last CriPec®docetaxel administration (EOT visit). In addition, ongoing SAEs were assessed at the 28-day FU, regardless of its relationship to the IMP.

Adverse event reporting additional description:

AEs occurring after EOT and coming to the attention of the Investigator must be recorded only if they are considered (in the opinion of the Investigator) related to CriPec®docetaxel.

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

Dictionary used

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

| | |
|--------------------|----|
| Dictionary version | 23 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Overall trial |
|-----------------------|---------------|

Reporting group description:

Subjects eligible for the trial received CriPec®docetaxel Q3W at the RP2D of 60 mg/m². Each treatment cycle consisted of 21 days. On Day 1 of each cycle, a single dose of CriPec®docetaxel was administered IV at a constant rate for ~1 hour. Pre-treatment with dexamethasone 8.0 mg orally was given three times before each CriPec®docetaxel administration (night before, morning and 1 hour before treatment).

Stage 1: (N=13) Simon 2-stage design.

Stage 2: (N=12). Simon 2-stage design no longer applicable. Maximum allowed treatment lines reduced from 3 to 2 lines, in both cases of which one could have been taxane-based. Life expectancy requirement extended from 12 weeks to 5 months.

| Serious adverse events | Overall trial | | |
|---|------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 16 / 25 (64.00%) | | |
| number of deaths (all causes) | 9 | | |
| number of deaths resulting from adverse events | 1 | | |
| Investigations | | | |
| Medical observation | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant ascites | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| T-cell prolymphocytic leukaemia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Social circumstances | | | |
| Social stay hospitalisation | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Ascites | | | |
| subjects affected / exposed | 4 / 25 (16.00%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Faecaloma | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhagic ascites | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 6 / 25 (24.00%) | | |
| occurrences causally related to treatment / all | 1 / 6 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pleural effusion | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Empyema | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Overall trial | | |
|---|-------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 25 / 25 (100.00%) | | |
| Nervous system disorders | | | |
| Dysgeusia | | | |
| subjects affected / exposed | 5 / 25 (20.00%) | | |
| occurrences (all) | 5 | | |
| Headache | | | |
| subjects affected / exposed | 3 / 25 (12.00%) | | |
| occurrences (all) | 3 | | |
| General disorders and administration site conditions | | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |
| Fatigue | | | |
| subjects affected / exposed | 11 / 25 (44.00%) | | |
| occurrences (all) | 17 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 6 / 25 (24.00%) | | |
| occurrences (all) | 7 | | |

| | | | |
|---|------------------------|--|--|
| Malaise subjects affected / exposed occurrences (all) | 4 / 25 (16.00%) 4 | | |
| Peripheral swelling subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 2 | | |
| Pyrexia subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 2 | | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 5 / 25 (20.00%) 10 | | |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 3 | | |
| Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) | 12 / 25 (48.00%) 18 | | |
| Vomiting subjects affected / exposed occurrences (all) | 9 / 25 (36.00%) 15 | | |
| Ascites subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 2 | | |
| Small intestinal obstruction subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | | |
| Intestinal obstruction subjects affected / exposed occurrences (all) | 3 / 25 (12.00%) 3 | | |
| Haemorrhagic ascites subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | | |
| Diarrhoea | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 5 / 25 (20.00%) | | |
| occurrences (all) | 9 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 4 / 25 (16.00%) | | |
| occurrences (all) | 5 | | |
| Constipation | | | |
| subjects affected / exposed | 4 / 25 (16.00%) | | |
| occurrences (all) | 5 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 3 / 25 (12.00%) | | |
| occurrences (all) | 3 | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | | |
| occurrences (all) | 2 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | | |
| occurrences (all) | 2 | | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | | |
| occurrences (all) | 2 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pleural effusion | | | |
| subjects affected / exposed | 4 / 25 (16.00%) | | |
| occurrences (all) | 4 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 10 / 25 (40.00%) | | |
| occurrences (all) | 12 | | |
| Cough | | | |
| subjects affected / exposed | 4 / 25 (16.00%) | | |
| occurrences (all) | 4 | | |
| Dysphonia | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | | |
| occurrences (all) | 2 | | |
| Epistaxis | | | |

| | | | |
|--|----------------------|--|--|
| subjects affected / exposed occurrences (all) | 3 / 25 (12.00%) 3 | | |
| Skin and subcutaneous tissue disorders | | | |
| Erythema | | | |
| subjects affected / exposed | 3 / 25 (12.00%) | | |
| occurrences (all) | 3 | | |
| Palmar-plantar erythrodysesthesia syndrome | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | | |
| occurrences (all) | 3 | | |
| Alopecia | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | | |
| occurrences (all) | 2 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Muscle spasms | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | | |
| occurrences (all) | 3 | | |
| Back pain | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | | |
| occurrences (all) | 2 | | |
| Infections and infestations | | | |
| Cystitis | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | | |
| occurrences (all) | 2 | | |
| Oral candidiasis | | | |

| | | | |
|--|---------------------|--|--|
| subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 2 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 9 / 25 (36.00%) | | |
| occurrences (all) | 15 | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | | |
| occurrences (all) | 4 | | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 3 / 25 (12.00%) | | |
| occurrences (all) | 4 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 11 September 2018 | <p>Protocol V3.0_25Sep2018 (NL, UK) and V2.0_11Sep2018 (Belgium-specific).</p> <p>For both UK and BE these protocols were approved under the Initial study approval. For NL it has been an amendment (SA01). The changes compared to V1.0_01Jun2018 include administrative changes and changes as directed by the CA of BE:</p> <ul style="list-style-type: none">-Frequency of pregnancy tests increased for women of childbearing potential-Further specification of footnotes of the schedule of assessments-Removal of some biochemistry parameters-Specification of the moment of EOT-Specification about SAE FU at safety FU visit |
| 28 May 2019 | <p>Protocol V4.0_20May2019 & Protocol V5.0_24Jun2019 after comments of the CA of NL</p> <p>The protocol was amended after data review of the first stage of the trial. The following changes were applied in protocol V4.0:</p> <ul style="list-style-type: none">- Modification of inclusion criterion maximum number of treatment lines allowed to match those of landmark docetaxel trials-Required life expectancy increased from 12 weeks to 5 months-Therefore no longer a Simon 2-stage study design-Updated dose modification criteria-Introduction of possibility to replace subjects under certain conditions-Change of scan interval changed from: SCR, after 6 weeks and every 12 weeks thereafter, to: SCR, after 9 weeks and every 9 weeks thereafter;-Updated safety information from previous trials IB V5.0;-Introduction of slot reservation process prior to subject registration;-Cap of 2 patients per site for the first 8 included patients to ensure balanced recruitment. <p>In protocol V5.0, a limit to the number of patients that may be replaced (max. 7) was introduced following comments from the CA in NL. Protocol V5.0 was submitted as a notification to UK and BE to ensure the same protocol version was used in all participating countries.</p> |
| 17 March 2020 | <p>Investigator's Brochure March2020</p> <ul style="list-style-type: none">-Updated trial status-Updated reference safety information |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|------|--------------|--------------|
|------|--------------|--------------|

| | | |
|---------------|--|---|
| 16 March 2020 | In light of the COVID-19 pandemic and the increased pressure on sites because of this, recruitment of patients was halted as of 16Mar2020. On 14May2020 it was subsequently decided that recruitment would not be resumed for the rest of the trial. The latter decision was communicated to sites on 18May2020, and was based on a DRC meeting held in April 2020, where efficacy signals were not considered strong enough to substantiate continuation. Patients that were on treatment during the time of the recruitment stop that was announced 16Mar2020 continued to receive treatment per protocol. At the time of the definitive recruitment closure on 18May2020, active patients (n=1) were informed of the limited efficacy signals and were given the choice to either continue or stop the treatment. | - |
|---------------|--|---|

Notes:

Limitations and caveats

None reported