



Clinical trial results:

Randomised Phase II Study comparing, as first-line chemotherapy, single-agent Oral Vinorelbine administered with two different schedules (metronomic and weekly schedules) in patients with Advanced Breast Cancer.

Summary

| | |
|--------------------------|----------------------|
| EudraCT number | 2014-003860-19 |
| Trial protocol | PT ES AT HU RO CZ DE |
| Global end of trial date | 28 September 2020 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 03 October 2021 |
| First version publication date | 03 October 2021 |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | PM0259CA233B0 |
|-----------------------|---------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Pierre Fabre Médicament |
| Sponsor organisation address | 45 place Abel Gance, Boulogne , France, 92100 |
| Public contact | Christine TA THANH MINH, PIERRE FABRE MEDICAMENT, +33 (0)149108121, christine.ta.thanh.minh@pierre-fabre.com |
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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 | 07 November 2019 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 September 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the Disease Control Rate (CR + PR + SD) in both arms (metronomic and weekly schedules) assessed during study treatments.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the current Declaration of Helsinki and was consistent with International Conference on Harmonisation Good Clinical practice (ICH GCP) and applicable regulatory requirements. The study was conducted in compliance with the protocol. The protocol, amendments, the subject information leaflet and the subject informed consent were approved by the appropriate independent Ethics Committee(s) in the involved countries prior to implementation.

Background therapy:

Preventive medication with an oral 5-HT3 antagonist was recommended before each oral vinorelbine administration. The primary prophylactic use of Colony Stimulating Factor (CSF) was allowed during the treatment period. Granulocyte stimulating growth factors were permitted for patients experiencing febrile neutropenia, Grade 4 asymptomatic neutropenia or neutropenic infection, according to institutional rules. Pre-menopausal patients were allowed to receive LHRH analogues in order to block ovarian functions. Patients received full supportive care throughout the study, including treatment when required with antibiotics, anti-diarrhoeals, analgesics, antiemetics, and transfusion of blood products, according to local guidelines and the investigator's opinion. Treatment with a bisphosphonate was allowed during the study period.

Evidence for comparator:

This study evaluated two schedules of administration of oral vinorelbine: the metronomic and the weekly schedules. The currently registered and approved regimen of Oral Vinorelbine delivered in a weekly schedule was used as reference arm.

| | |
|---|----------------|
| Actual start date of recruitment | 03 August 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 | Italy: 21 |
| Country: Number of subjects enrolled | Poland: 29 |
| Country: Number of subjects enrolled | Portugal: 16 |
| Country: Number of subjects enrolled | Romania: 4 |
| Country: Number of subjects enrolled | Spain: 49 |
| Country: Number of subjects enrolled | Austria: 5 |
| Country: Number of subjects enrolled | Czechia: 5 |
| Country: Number of subjects enrolled | France: 22 |
| Country: Number of subjects enrolled | Germany: 3 |

| | |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Hungary: 9 |
| Worldwide total number of subjects | 163 |
| EEA total number of subjects | 163 |

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) | 76 |
| From 65 to 84 years | 83 |
| 85 years and over | 4 |

Subject disposition

Recruitment

Recruitment details:

A total of 43 centres in 10 countries screened 218 hormone-receptor-positive (HRc) and HER2 negative patients with advanced breast cancer between the 22 of December 2015 and the 13 of December 2017. Of these 218 patients, 164 patients were randomised and 163 patients received at least one dose of study drug.

Pre-assignment

Screening details:

A 28-day screening period was planned before randomisation and screened HRc-positive and HER2 negative patients with advanced breast cancer. Once the screening period was successfully completed, patients who fulfilled the eligibility criteria were randomised in a 1:1 ratio in the 2 arms.

Period 1

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

Arms

| | |
|------------------------------|----------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Arm A: metronomic schedule |

Arm description:

Patients received Oral Vinorelbine at metronomic schedules, i.e. three times weekly.

| | |
|--|------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Oral vinorelbine |
| Investigational medicinal product code | |
| Other name | Navelbine |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Patients received a fixed dose of 50 mg of Oral Vinorelbine (one capsule of 20mg plus one of 30mg) three times weekly (on Mondays, Wednesdays and Fridays or Tuesdays, Thursdays and Saturdays) continuously until disease progression, unacceptable toxicity, patient's refusal or investigator's decision. Each 3 weeks of treatment was considered as a separate cycle, therefore in Treatment Arm A, a cycle consisted of 9 fixed doses of 50 mg at days 1, 3, 5, 8, 10, 12, 15, 17 and 19.

| | |
|------------------|------------------------|
| Arm title | Arm B: weekly schedule |
|------------------|------------------------|

Arm description:

Patients received Oral Vinorelbine at weekly schedules, i.e. once a week.

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Oral vinorelbine |
| Investigational medicinal product code | |
| Other name | Navelbine |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Patients received Oral Vinorelbine at the dose of 60 mg/m² on day 1, day 8 and day 15 of the first cycle. At the second and following cycles, the day 1, day 8 and day 15 were increased to 80 mg/m², according to haematological tolerance. The dosage was calculated according to BSA, using the Dubois and Dubois formula. Treatment was administered until disease progression, unacceptable toxicity, patient's refusal or investigator's decision. Each 3 weeks of treatment was considered a cycle, therefore in Treatment Arm B a cycle consisted of 3 doses at days 1, 8 and 15.

| Number of subjects in period 1 | Arm A: metronomic schedule | Arm B: weekly schedule |
|---------------------------------------|----------------------------|------------------------|
| Started | 82 | 81 |
| Completed | 0 | 2 |
| Not completed | 82 | 79 |
| Physician decision | 2 | 4 |
| Adverse event, non-fatal | 7 | 10 |
| Other | 5 | 3 |
| Progressive disease | 68 | 57 |
| Withdrawal by subject | - | 5 |

Baseline characteristics

Reporting groups

| | |
|--|----------------------------|
| Reporting group title | Arm A: metronomic schedule |
| Reporting group description: | |
| Patients received Oral Vinorelbine at metronomic schedules, i.e. three times weekly. | |
| Reporting group title | Arm B: weekly schedule |
| Reporting group description: | |
| Patients received Oral Vinorelbine at weekly schedules, i.e. once a week. | |

| Reporting group values | Arm A: metronomic schedule | Arm B: weekly schedule | Total |
|--------------------------------------|----------------------------|------------------------|-------|
| Number of subjects | 82 | 81 | 163 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 42 | 34 | 76 |
| From 65-84 years | 37 | 46 | 83 |
| 85 years and over | 3 | 1 | 4 |
| Age continuous | | | |
| Units: years | | | |
| median | 64 | 66 | |
| full range (min-max) | 42 to 89 | 38 to 87 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 82 | 81 | 163 |
| Male | 0 | 0 | 0 |
| Karnofsky performance status (KPS) | | | |
| Units: Subjects | | | |
| 70% | 5 | 4 | 9 |
| 80% | 22 | 18 | 40 |
| 90% | 22 | 27 | 49 |
| 100% | 33 | 32 | 65 |
| Histological type at first diagnosis | | | |
| Units: Subjects | | | |
| Carcinoma | 24 | 27 | 51 |
| Ductal | 45 | 41 | 86 |
| Lobular | 10 | 12 | 22 |
| Inflammatory | 0 | 0 | 0 |
| Other | 3 | 0 | 3 |
| Unknown | 0 | 1 | 1 |
| Number of organs involved | | | |
| Units: Subjects | | | |
| 01 | 11 | 12 | 23 |
| 02 | 33 | 31 | 64 |
| >=3 | 38 | 38 | 76 |
| Cancer stage at first diagnosis | | | |
| Units: Subjects | | | |
| IA | 7 | 9 | 16 |
| IB | 0 | 1 | 1 |

| | | | |
|--|--------------|--------------|----|
| IIA | 15 | 16 | 31 |
| IIB | 16 | 19 | 35 |
| IIIA | 15 | 10 | 25 |
| IIIB | 3 | 5 | 8 |
| IIIC | 6 | 7 | 13 |
| IV | 17 | 12 | 29 |
| Missing | 3 | 2 | 5 |
| Primary tumor site | | | |
| Units: Subjects | | | |
| Right breast | 44 | 41 | 85 |
| Left breast | 35 | 37 | 72 |
| Bilateral breast | 3 | 3 | 6 |
| Histological grade at first diagnosis | | | |
| Units: Subjects | | | |
| SBR I | 7 | 6 | 13 |
| SBR II | 31 | 33 | 64 |
| SBR III | 18 | 12 | 30 |
| Unknown | 26 | 30 | 56 |
| Body mass index | | | |
| Units: kg/m ² | | | |
| arithmetic mean | 27.3 | 27.3 | |
| standard deviation | ± 5.25 | ± 5.17 | - |
| Time between diagnosis and randomisation | | | |
| Units: months | | | |
| median | 67.65 | 78.00 | |
| full range (min-max) | 2.4 to 321.1 | 2.0 to 327.5 | - |

End points

End points reporting groups

| | |
|--|----------------------------|
| Reporting group title | Arm A: metronomic schedule |
| Reporting group description: | |
| Patients received Oral Vinorelbine at metronomic schedules, i.e. three times weekly. | |
| Reporting group title | Arm B: weekly schedule |
| Reporting group description: | |
| Patients received Oral Vinorelbine at weekly schedules, i.e. once a week. | |

Primary: Disease control rate (DCR)

| | |
|--|---|
| End point title | Disease control rate (DCR) ^[1] |
| End point description: | |
| DCR, defined as the sum of CR, PR and SD rates was observed in 52/82 patients (63.4% [95% CI: 52.0, 73.8]) in Arm A and 59/81 patients (72.8% [95% CI: 61.8, 82.1]) in Arm B. | |
| End point type | Primary |
| End point timeframe: | |
| DCR according to investigator was calculated among the BOCR responders in the ITT analysis set on the treatment period (from the date of randomisation until the documentation of progression or death due to any cause. | |

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 study was designed to evaluate the disease control rate in each arm of oral vinorelbine but not to compare the two schedules (metronomic / weekly). No statistical analysis was performed on the primary efficacy endpoint

| End point values | Arm A: metronomic schedule | Arm B: weekly schedule | | |
|----------------------------------|----------------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 82 | 81 | | |
| Units: percentage | | | | |
| number (confidence interval 95%) | 63.4 (52.0 to 73.8) | 72.8 (61.8 to 82.1) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of disease control

| | |
|---|-----------------------------|
| End point title | Duration of disease control |
| End point description: | |
| Overall, for patients who achieved PR or SD (no CR was observed in any arm), 43 (82.7%) patients in Arm A and 44 (74.6%) patients in Arm B experienced disease progression or death. The median time to disease progression or death was 6.9 months (95% CI: 4.2, 8.6) in Arm A and 7.9 months (95% CI: 5.7, 10.0) in Arm B. The distribution of DCR was described by treatment arm using Kaplan-Meier methods, reporting estimated median (in months) with 95% CI, 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at several time points. | |
| End point type | Secondary |

End point timeframe:

Duration of disease control was defined as the period from the date of randomisation until date of PD or death from any cause, whichever occurred first. Only responders (patients with BOCR of CR or PR) and stable patients were included in the analysis.

| End point values | Arm A: metronomic schedule | Arm B: weekly schedule | | |
|----------------------------------|----------------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 52 | 59 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 6.9 (4.2 to 8.6) | 7.9 (5.7 to 10.0) | | |

| | |
|-----------------------------------|---|
| Attachments (see zip file) | Duration of disease control (months)/14_2_1_1_FIG.rtf |
|-----------------------------------|---|

Statistical analyses

No statistical analyses for this end point

Secondary: DCR without grade 3-4 toxicity

| | |
|---|--------------------------------|
| End point title | DCR without grade 3-4 toxicity |
| End point description: DCR without grade 3-4 toxicity, defined as the sum of CR, PR and SD without grade 3-4 toxicity rates, was observed in 24/82 patients (29.3% [95% CI: 19.7, 40.4]) in Arm A and 18/81 patients (22.2% [95% CI: 13.7, 32.8]) in Arm B. | |
| End point type | Secondary |
| End point timeframe: DCR without grade 3-4 toxicity was calculated among the BOCR responders and stable patients without grade 3-4 toxicity in the ITT population from the date of randomisation until the documentation of progression or death or first grade 3 or 4 AE. | |

| End point values | Arm A: metronomic schedule | Arm B: weekly schedule | | |
|----------------------------------|----------------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 82 | 81 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 29.3 (19.7 to 40.4) | 22.2 (13.7 to 32.8) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: DCR without grade 3-4 neutropenia

| | |
|-----------------|-----------------------------------|
| End point title | DCR without grade 3-4 neutropenia |
|-----------------|-----------------------------------|

End point description:

DCR without grade 3-4 neutropenia, defined as the sum of CR, PR and SD without grade 3-4 neutropenia rates, was observed in 35/82 patients (42.7% [95% CI: 31.8, 54.1]) in Arm A and 25/81 patients (30.9% [95% CI: 21.1, 42.1]) in Arm B.

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

End point timeframe:

DCR without grade 3-4 neutropenia was calculated among the BOCR responders and stable patients without grade 3-4 neutropenia in the ITT population from the date of randomisation until the documentation of progression, first grade 3-4 neutropenia or death.

| End point values | Arm A: metronomic schedule | Arm B: weekly schedule | | |
|----------------------------------|----------------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 82 | 81 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 42.7 (31.8 to 54.1) | 30.9 (21.1 to 42.1) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR)

| | |
|-----------------|-------------------------------|
| End point title | Objective Response Rate (ORR) |
|-----------------|-------------------------------|

End point description:

ORR, defined as the sum of CR and PR rates, was observed in 14/82 patients (17.1% [95% CI: 9.7, 27.0]) in Arm A and 17/81 patients (21.0% [95% CI: 12.7, 31.5]) in Arm B.

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

End point timeframe:

ORR according to investigator was calculated among the BOCR responders (CR and PR) in the ITT population from the date of randomisation until the documentation of progression or death.

| End point values | Arm A: metronomic schedule | Arm B: weekly schedule | | |
|----------------------------------|----------------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 82 | 81 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 17.1 (9.7 to 27.0) | 21.0 (12.7 to 31.5) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: ORR without grade 3-4 toxicity

| | |
|-----------------|--------------------------------|
| End point title | ORR without grade 3-4 toxicity |
|-----------------|--------------------------------|

End point description:

ORR without grade 3-4 toxicity, defined as the sum of CR and PR without grade 3-4 toxicity rates, was observed in 8/82 patients (9.8% [95% CI: 4.3, 18.3]) in Arm A and 6/81 patients (7.4% [95% CI: 2.8, 15.4]) in Arm B.

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

End point timeframe:

ORR without grade 3-4 toxicity was calculated among the BOCR responders (CR and PR) who had not experienced grade 3-4 toxicity in the ITT population from the date of randomisation until the documentation of progression, first grade 3 or 4 AE or death.

| End point values | Arm A: metronomic schedule | Arm B: weekly schedule | | |
|----------------------------------|----------------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 82 | 81 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 9.8 (4.3 to 18.3) | 7.4 (2.8 to 15.4) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: ORR without grade 3-4 neutropenia

| | |
|-----------------|-----------------------------------|
| End point title | ORR without grade 3-4 neutropenia |
|-----------------|-----------------------------------|

End point description:

ORR without grade 3-4 neutropenia, defined as the sum of CR and PR without grade 3-4 neutropenia rates, was observed in 10/82 patients (12.2% [95% CI: 6.0, 21.3]) in Arm A and 6/81 patients (7.4% [95% CI: 2.8, 15.4]) in Arm B.

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

End point timeframe:

ORR without grade 3-4 neutropenia was calculated among the BOCR responders (CR and PR) who hadn't experienced grade 3-4 neutropenia in the ITT population from the date of randomisation until the documentation of PD, first grade 3-4 neutropenia or death

| End point values | Arm A: metronomic schedule | Arm B: weekly schedule | | |
|----------------------------------|----------------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 82 | 81 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 12.2 (6.0 to 21.3) | 7.4 (2.8 to 15.4) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DOR)

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

End point description:

Overall, for patients who achieved PR (no CR was observed in any arm), 12 (85.7%) patients in Arm A and 10 (58.8%) patients in Arm B experienced disease progression or death. The median DOR was 8.5 months (95% CI: 4.2, 11.4) in Arm A and 9.3 months (95% CI: 6.8, 19.2) in Arm B. The distribution of duration of response was described by treatment arm using Kaplan-Meier methods, reporting estimated median (in months) with 95% CI, 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at several time points.

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

End point timeframe:

Duration of response was calculated among the BOCR responders (CR and PR) in the ITT population from the date of randomisation until the documentation of progression or death from any cause, whichever occurred first.

| End point values | Arm A: metronomic schedule | Arm B: weekly schedule | | |
|----------------------------------|----------------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 14 | 17 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 8.5 (4.2 to 11.4) | 9.3 (6.8 to 19.2) | | |

| | |
|-----------------------------------|--|
| Attachments (see zip file) | Duration of response (months) (ITT analysis set) |
|-----------------------------------|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first response

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|-----------------|------------------------|
| End point title | Time to first response |
|-----------------|------------------------|

End point description:

Overall, 14 patients in Arm A and 17 patients in Arm B achieved a PR (no CR). The median Time to first

response was 2.8 months (95% CI: 1.3, 3.9) in Arm A and 2.8 months (95% CI: 1.4, 4.2) in Arm B. The distribution of Time to first response was described by treatment arm using Kaplan-Meier methods, reporting estimated median (in months) with 95% CI, 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at several time points.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Time to first response, defined as the time from the date of randomisation to the date of first CR or PR after randomisation, whichever occurred first was measured until the documentation of progression or death from any cause, whichever occurred first. | |

| End point values | Arm A: metronomic schedule | Arm B: weekly schedule | | |
|----------------------------------|----------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 14 | 17 | | |
| Units: month | | | | |
| median (confidence interval 95%) | 2.8 (1.3 to 3.9) | 2.8 (1.4 to 4.2) | | |

| | |
|-----------------------------------|--|
| Attachments (see zip file) | Time to first response (months) (ITT analysis set) |
|-----------------------------------|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of stable disease

| | |
|--|----------------------------|
| End point title | Duration of stable disease |
| End point description: | |
| A total of 38 patients in Arm A and 42 patients in Arm B achieved SD. Of these, 31 (81.6%) patients in Arm A and 34 (81.0%) patients in Arm B experienced disease progression or death. The median duration of SD was 4.2 months (95% CI: 4.0, 6.7) in Arm A and 5.7 months (95% CI: 5.0, 7.8) in Arm B. The distribution of duration of stable disease was described by treatment arm using Kaplan-Meier methods, reporting estimated median (in months) with 95% CI, 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at several time points. | |
| End point type | Secondary |
| End point timeframe: | |
| Duration of Stable Disease was measured from the date of randomisation until the date of PD or death from any cause, whichever occurred first. | |

| End point values | Arm A: metronomic schedule | Arm B: weekly schedule | | |
|----------------------------------|----------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 38 | 42 | | |
| Units: month | | | | |
| median (confidence interval 95%) | 4.2 (4.0 to 6.7) | 5.7 (5.0 to 7.8) | | |

| | |
|-----------------------------------|--|
| Attachments (see zip file) | Duration of stable disease (months) (ITT analysis) |
|-----------------------------------|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS)

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|-----------------|---------------------------------|
| End point title | Progression-free survival (PFS) |
|-----------------|---------------------------------|

End point description:

Overall, disease progression or death was reported in 80/82 (97.6%) patients in Arm A and 73/81 (90.1%) patients in Arm B. The median PFS was 4.0 months (95% CI: 2.8, 5.4) in Arm A and 5.6 months (95% CI: 4.4, 7.8) in Arm B. The distribution of progression-free survival was described by treatment arm using Kaplan-Meier methods, reporting estimated median (in months) with 95% CI, 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at several time points.

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

End point timeframe:

The progression-free survival (PFS) was measured from randomisation until the first radiographically documented progression of disease or death from any cause, whichever occurred first.

| End point values | Arm A: metronomic schedule | Arm B: weekly schedule | | |
|----------------------------------|----------------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 82 | 81 | | |
| Units: month | | | | |
| median (confidence interval 95%) | 4.0 (2.8 to 5.4) | 5.6 (4.4 to 7.8) | | |

| | |
|-----------------------------------|--|
| Attachments (see zip file) | PFS (months) (ITT analysis set)/14_2_5_1_FIG.rtf |
|-----------------------------------|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival without grade 3-4 toxicity

| | |
|-----------------|--|
| End point title | Progression-free survival without grade 3-4 toxicity |
|-----------------|--|

End point description:

Overall, grade 3-4 toxicity, disease progression or death was reported in 77 (93.9%) patients in Arm A and 74 (91.4%) patients in Arm B. The median PFS without grade 3-4 toxicity was 1.7 months (95% CI: 1.4, 2.8) in Arm A and 1.4 months (95% CI: 1.3, 2.1) in Arm B. The distribution of Progression-free survival without grade 3-4 toxicity was described by treatment arm using Kaplan-Meier methods, reporting estimated median (in months) with 95% CI, 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at several time points.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| PFS without grade 3-4 toxicity was measured from randomisation until the first radiographically documented progression of disease, first AE with grade 3 or 4 toxicity or death from any cause, whichever occurred first. | |

| End point values | Arm A: metronomic schedule | Arm B: weekly schedule | | |
|----------------------------------|----------------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 82 | 81 | | |
| Units: month | | | | |
| median (confidence interval 95%) | 1.7 (1.4 to 2.8) | 1.4 (1.3 to 2.1) | | |

| | |
|-----------------------------------|--|
| Attachments (see zip file) | PFS without grade 3-4 toxicity (months)/14_2_6_1_FIG.rtf |
|-----------------------------------|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival without grade 3-4 neutropenia

| | |
|--|---|
| End point title | Progression-free survival without grade 3-4 neutropenia |
| End point description: | |
| Overall, grade 3-4 neutropenia, disease progression or death was reported in 76 (92.7%) patients in Arm A and 70 (86.4%) patients in Arm B. The median PFS without grade 3-4 neutropenia was 2.7 months (95% CI: 1.4, 3.9) in Arm A and 2.1 months (95% CI: 1.4, 2.6) in Arm B. The distribution of Progression-free survival without grade 3-4 neutropenia was described by treatment arm using Kaplan-Meier methods, reporting estimated median (in months) with 95% CI, 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at several time points. | |
| End point type | Secondary |
| End point timeframe: | |
| PFS without grade 3-4 neutropenia was measured from randomisation until the first radiographically documented progression of disease, first grade 3 or 4 neutropenia or death from any cause, whichever occurred first. | |

| End point values | Arm A: metronomic schedule | Arm B: weekly schedule | | |
|----------------------------------|----------------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 82 | 81 | | |
| Units: month | | | | |
| median (confidence interval 95%) | 2.7 (1.4 to 3.9) | 2.1 (1.4 to 2.6) | | |

| | |
|-----------------------------------|---|
| Attachments (see zip file) | Progression-free survival without grade 3-4 |
|-----------------------------------|---|

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

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

End point description:

Death was reported in 50 (61.0%) patients in Arm A and 42 (51.9%) patients in Arm B. Median OS were 22.3 months (95% CI: 19.0, 27.3) in Arm A and 26.7 months (95% CI: 22.2, 37.8) in Arm B. The distribution of Overall Survival was described by treatment arm using Kaplan-Meier methods, reporting estimated median (in months) with 95% CI, 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at several time points.

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

End point timeframe:

Overall survival was measured from the date of randomisation until the date of death, regardless of the cause of death.

| End point values | Arm A: metronomic schedule | Arm B: weekly schedule | | |
|----------------------------------|----------------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 82 | 81 | | |
| Units: month | | | | |
| median (confidence interval 95%) | 22.3 (19.0 to 27.3) | 26.7 (22.2 to 37.8) | | |

| | |
|-----------------------------------|---|
| Attachments (see zip file) | Overall survival (months) (ITT analysis set)/14_2_9_1_FIG.rtf |
|-----------------------------------|---|

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any AE that first occurred during the treatment period (i.e. from first study treatment administration date up to last administration date + 30 days) was recorded in the CRF and included in the analysis of AEs (on-study AE).

Adverse event reporting additional description:

At the cut-off date (07-NOV-2019), 2 patients were still on treatment. Death was reported for 88 patients, while 60 patients were still being followed for survival. Four patients were lost to follow-up. All patients in the safety analysis set received at least one cycle with a median number of cycle of 4.0 (1-41) in Arm A and 7.0 (1-45) in Arm B.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 22.0 |

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Arm A: metronomic schedule (Safety analysis set) |
|-----------------------|--|

Reporting group description:

All patients who received at least one dose of study drug and with at least one post-baseline safety data were included in the safety analysis set. A total of 82 patients were included in the safety analysis set.

| | |
|-----------------------|--|
| Reporting group title | Arm B: weekly schedule (Safety analysis set) |
|-----------------------|--|

Reporting group description:

All patients who received at least one dose of study drug and with at least one post-baseline safety data were included in the safety analysis set. A total of 80 patients were included in the safety analysis set.

| Serious adverse events | Arm A: metronomic schedule (Safety analysis set) | Arm B: weekly schedule (Safety analysis set) | |
|---|--|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 22 / 82 (26.83%) | 13 / 80 (16.25%) | |
| number of deaths (all causes) | 50 | 42 | |
| number of deaths resulting from adverse events | 2 | 4 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 80 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Vascular disorders | | | |
| Jugular vein thrombosis | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 80 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subclavian vein thrombosis | | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 80 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 80 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 1 / 80 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 1 / 80 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden death | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 80 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthmatic crisis | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 80 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 82 (2.44%) | 0 / 80 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydrothorax | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 80 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 2 / 80 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 80 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 80 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 80 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 80 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 80 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 80 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Atrioventricular block complete | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 82 (0.00%) | 1 / 80 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Nervous system disorders | | | |
| Neuroglycopenia | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 80 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Somnolence | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 1 / 80 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 1 / 80 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 2 / 80 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 2 / 82 (2.44%) | 0 / 80 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Ascites | | | |
| subjects affected / exposed | 2 / 82 (2.44%) | 0 / 80 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocolitis | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 80 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Intestinal obstruction | | | |
| subjects affected / exposed | 2 / 82 (2.44%) | 0 / 80 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 1 / 80 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic colitis | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 1 / 80 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 1 / 80 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholangitis acute | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 1 / 80 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic failure | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 80 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 80 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Decubitus ulcer | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 1 / 80 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Musculoskeletal and connective tissue disorders | | | |
| Bone pain | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 1 / 80 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Mastitis | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 80 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 1 / 80 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 1 / 80 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 3 / 82 (3.66%) | 0 / 80 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 1 / 80 (1.25%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 1 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 80 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 1 / 80 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Metabolism and nutrition disorders | | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 1 / 80 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Arm A: metronomic schedule (Safety analysis set) | Arm B: weekly schedule (Safety analysis set) | |
|---|--|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 79 / 82 (96.34%) | 78 / 80 (97.50%) | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 4 / 80 (5.00%) | |
| occurrences (all) | 1 | 5 | |
| Weight decreased | | | |
| subjects affected / exposed | 28 / 82 (34.15%) | 35 / 80 (43.75%) | |
| occurrences (all) | 37 | 57 | |
| Weight increased | | | |
| subjects affected / exposed | 3 / 82 (3.66%) | 5 / 80 (6.25%) | |
| occurrences (all) | 3 | 5 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 5 / 82 (6.10%) | 4 / 80 (5.00%) | |
| occurrences (all) | 6 | 4 | |
| Nervous system disorders | | | |
| Dysgeusia | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 5 / 80 (6.25%) | |
| occurrences (all) | 1 | 6 | |
| Headache | | | |
| subjects affected / exposed | 3 / 82 (3.66%) | 9 / 80 (11.25%) | |
| occurrences (all) | 3 | 9 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 5 / 82 (6.10%) | 4 / 80 (5.00%) | |
| occurrences (all) | 5 | 14 | |

| | | | |
|--|------------------|------------------|--|
| Neutropenia | | | |
| subjects affected / exposed | 28 / 82 (34.15%) | 57 / 80 (71.25%) | |
| occurrences (all) | 64 | 175 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 4 / 80 (5.00%) | |
| occurrences (all) | 2 | 7 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 16 / 82 (19.51%) | 26 / 80 (32.50%) | |
| occurrences (all) | 38 | 57 | |
| Fatigue | | | |
| subjects affected / exposed | 13 / 82 (15.85%) | 11 / 80 (13.75%) | |
| occurrences (all) | 17 | 15 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 2 / 82 (2.44%) | 6 / 80 (7.50%) | |
| occurrences (all) | 2 | 8 | |
| Pyrexia | | | |
| subjects affected / exposed | 6 / 82 (7.32%) | 9 / 80 (11.25%) | |
| occurrences (all) | 7 | 11 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 8 / 82 (9.76%) | 8 / 80 (10.00%) | |
| occurrences (all) | 10 | 14 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 7 / 82 (8.54%) | 9 / 80 (11.25%) | |
| occurrences (all) | 9 | 11 | |
| Constipation | | | |
| subjects affected / exposed | 14 / 82 (17.07%) | 14 / 80 (17.50%) | |
| occurrences (all) | 16 | 17 | |
| Diarrhoea | | | |
| subjects affected / exposed | 23 / 82 (28.05%) | 30 / 80 (37.50%) | |
| occurrences (all) | 30 | 91 | |
| Dyspepsia | | | |
| subjects affected / exposed | 5 / 82 (6.10%) | 3 / 80 (3.75%) | |
| occurrences (all) | 7 | 3 | |
| Nausea | | | |

| | | | |
|---|---|---|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vomiting</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>27 / 82 (32.93%)</p> <p>55</p> <p>8 / 82 (9.76%)</p> <p>14</p> | <p>44 / 80 (55.00%)</p> <p>99</p> <p>31 / 80 (38.75%)</p> <p>46</p> | |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dyspnoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>3 / 82 (3.66%)</p> <p>3</p> <p>8 / 82 (9.76%)</p> <p>17</p> | <p>4 / 80 (5.00%)</p> <p>5</p> <p>4 / 80 (5.00%)</p> <p>5</p> | |
| <p>Skin and subcutaneous tissue disorders</p> <p>Alopecia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Rash</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>3 / 82 (3.66%)</p> <p>4</p> <p>0 / 82 (0.00%)</p> <p>0</p> | <p>9 / 80 (11.25%)</p> <p>14</p> <p>4 / 80 (5.00%)</p> <p>4</p> | |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Arthralgia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Back pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Bone pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pain in extremity</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>5 / 82 (6.10%)</p> <p>5</p> <p>8 / 82 (9.76%)</p> <p>11</p> <p>7 / 82 (8.54%)</p> <p>10</p> <p>2 / 82 (2.44%)</p> <p>2</p> | <p>6 / 80 (7.50%)</p> <p>6</p> <p>5 / 80 (6.25%)</p> <p>6</p> <p>7 / 80 (8.75%)</p> <p>8</p> <p>5 / 80 (6.25%)</p> <p>6</p> | |
| <p>Infections and infestations</p> <p>Nasopharyngitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>3 / 82 (3.66%)</p> <p>3</p> | <p>5 / 80 (6.25%)</p> <p>6</p> | |

| | | | |
|--|-----------------------|------------------------|--|
| Respiratory tract infection subjects affected / exposed occurrences (all) | 6 / 82 (7.32%) 7 | 1 / 80 (1.25%) 1 | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 1 / 82 (1.22%) 1 | 6 / 80 (7.50%) 7 | |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 9 / 82 (10.98%) 12 | 16 / 80 (20.00%) 19 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 05 November 2019 | <p>Considering all data collected during the time period of the study, the sponsor decided to anticipate the end of study and to proceed with the final statistical analysis earlier.</p> <p>This decision was based on the following considerations observed on September 10th, 2019:</p> <ul style="list-style-type: none">• After 45 months of study duration, among the 165 randomised patients (164 treated), 152 events (progression or death) were observed. For 12 randomised patients, neither disease progression nor death were recorded (1 patient never received the study drug, 3 patients did not yet progress, 4 drop out patients and 4 patients with only non-radiological progression), and 1 patient was removed from clinical database (no local data privacy form available).• The maturity of PFS data could thus be considered as being reached.• 85 deaths were observed, and it was estimated that maturity of OS data (i.e. at least 80% of events) would not be reached by the end-of-study (with the current definition in the protocol). The study was not designed to get mature OS data, however the median OS was reached. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported