



Clinical trial results:

PRESERVE 1: A Phase 3 Randomized, Double-blind Trial of Trilaciclib versus Placebo in Patients Receiving FOLFOXIRI/Bevacizumab for Metastatic Colorectal Cancer

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2019-003826-25 |
| Trial protocol | GB SK PL HU IT |
| Global end of trial date | 31 March 2023 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 22 May 2024 |
| First version publication date | 22 May 2024 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | G1T28-207 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04607668 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | G1 Therapeutics, Inc. |
| Sponsor organisation address | 700 Park Offices Drive, Suite 200, Research Triangle Park, United States, 27709 |
| Public contact | Clinical Trial Info, G1 Therapeutics, Inc., +1 919 213 9835, clinicalinfo@g1therapeutics.com |
| Scientific contact | Clinical Trial Info, G1 Therapeutics, Inc., +1 919 213 9835, clinicalinfo@g1therapeutics.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 | 31 March 2023 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 31 March 2023 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

To assess the effects of trilaciclib on the neutrophil lineage compared with placebo in participants receiving FOLFOXIRI/bevacizumab for proficient mismatch repair/microsatellite stable (pMMR/MSS) metastatic colorectal cancer (mCRC).

Protection of trial subjects:

This study was conducted in full conformance with the ethical principles of the Declaration of Helsinki (as amended in Tokyo, Venice, Hong Kong, and South Africa) or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. A Data Safety Monitoring Committee (DMC) reviewed safety of trilaciclib for all participants enrolled. The DMC monitored accumulating safety and disposition data approximately every 4 months. The committee consisted of individuals with extensive multicenter clinical study experience drawn from the fields of clinical oncology (specifically, CRC) and biostatistics. These individuals were entirely independent of the conduct of the study.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 16 October 2020 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 25 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Poland: 19 |
| Country: Number of subjects enrolled | Spain: 41 |
| Country: Number of subjects enrolled | United Kingdom: 13 |
| Country: Number of subjects enrolled | Hungary: 20 |
| Country: Number of subjects enrolled | Italy: 11 |
| Country: Number of subjects enrolled | China: 53 |
| Country: Number of subjects enrolled | Ukraine: 44 |
| Country: Number of subjects enrolled | United States: 125 |
| Worldwide total number of subjects | 326 |
| EEA total number of subjects | 91 |

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) | 244 |
| From 65 to 84 years | 82 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

A total of 82 sites enrolled participants in China, Hungary, Italy, Poland, Spain, Ukraine, United Kingdom and United States. The first participant was enrolled on 16 October 2020, and the last participant completed on 31 March 2023.

Pre-assignment

Screening details:

A total of 458 participants were screened in this study of which 132 were reported as screen failures. Thus, 326 participants were randomized in the study.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|-------------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Trilaciclib + FOLFOXIRI/Bevacizumab |

Arm description:

Participants received trilaciclib 240 milligram per meter square (mg/m²) on Days 1 and 2 administered intravenously (IV) prior to FOLFOXIRI (fluorouracil [5FU {infusional}], leucovorin, oxaliplatin, and irinotecan)/bevacizumab in 14-day cycles for up to 12 cycles (induction). Following completion of induction, participants continued in maintenance, where they received trilaciclib per randomization allocation at study entry. Trilaciclib was administered prior to infusional-5FU/leucovorin/bevacizumab at the same dose and schedule used during induction. Participants continued to receive treatment until disease progression, unacceptable toxicity, withdrawal of consent, discontinuation by Investigator, or the end of the trial, whichever occurred first.

| | |
|--|-----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Trilaciclib |
| Investigational medicinal product code | |
| Other name | G1T28 |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Trilaciclib 240 mg/m² was provided as a single-use, sterile powder to be reconstituted then diluted with 250 milliliter (mL) of dextrose 5% in water or normal saline (NaCl 0.9%).

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

Dosage and administration details:

Fluorouracil 2400 to 3200 mg/m², Leucovorin 400 mg/m² (LEVO leucovorin 200 mg/m² was an acceptable alternative), Oxaliplatin 85 mg/m² and Irinotecan 165 mg/m² was administered as Standard of Care (SOC) therapy.

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

Dosage and administration details:

Bevacizumab 5 mg/kilogram (kg) was administered as SOC therapy.

| | |
|------------------|---------------------------------|
| Arm title | Placebo + FOLFOXIRI/Bevacizumab |
|------------------|---------------------------------|

Arm description:

Participants received placebo on Days 1 and 2 administered IV prior to FOLFOXIRI/bevacizumab in 14-day cycles for up to 12 cycles (induction). Following completion of induction, participants continued in maintenance, where they received placebo per randomization allocation at study entry. Placebo was administered prior to infusional-5FU/leucovorin/bevacizumab at the same dose and schedule used during induction. Participants continued to receive treatment until disease progression, unacceptable toxicity, withdrawal of consent, discontinuation by Investigator, or the end of the trial, whichever occurred first.

| | |
|--|-----------------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Placebo was provided as 250 mL of dextrose 5% in water or normal saline (NaCl 0.9%).

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

Dosage and administration details:

Fluorouracil 2400 to 3200 mg/m², Leucovorin 400 mg/m² (LEVO leucovorin 200 mg/m² was an acceptable alternative), Oxaliplatin 85 mg/m² and Irinotecan 165 mg/m² was administered as SOC therapy.

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

Dosage and administration details:

Bevacizumab 5 mg/kilogram (kg) was administered as SOC therapy.

| Number of subjects in period 1 | Trilaciclib + FOLFOXIRI/Bevacizumab | Placebo + FOLFOXIRI/Bevacizumab |
|---------------------------------------|-------------------------------------|---------------------------------|
| Started | 164 | 162 |
| Completed | 0 | 0 |
| Not completed | 164 | 162 |
| Consent withdrawn by subject | 12 | 11 |
| Study terminated by Sponsor | 92 | 114 |
| Death | 49 | 26 |
| Unspecified | 8 | 7 |

| | | |
|-------------------|---|---|
| Lost to follow-up | 3 | 4 |
|-------------------|---|---|

Baseline characteristics

Reporting groups

| | |
|--|-------------------------------------|
| Reporting group title | Trilaciclib + FOLFOXIRI/Bevacizumab |
| Reporting group description: | |
| Participants received trilaciclib 240 milligram per meter square (mg/m ²) on Days 1 and 2 administered intravenously (IV) prior to FOLFOXIRI (fluorouracil [5FU {infusional}], leucovorin, oxaliplatin, and irinotecan)/bevacizumab in 14-day cycles for up to 12 cycles (induction). Following completion of induction, participants continued in maintenance, where they received trilaciclib per randomization allocation at study entry. Trilaciclib was administered prior to infusional-5FU/leucovorin/bevacizumab at the same dose and schedule used during induction. Participants continued to receive treatment until disease progression, unacceptable toxicity, withdrawal of consent, discontinuation by Investigator, or the end of the trial, whichever occurred first. | |
| Reporting group title | Placebo + FOLFOXIRI/Bevacizumab |
| Reporting group description: | |
| Participants received placebo on Days 1 and 2 administered IV prior to FOLFOXIRI/bevacizumab in 14-day cycles for up to 12 cycles (induction). Following completion of induction, participants continued in maintenance, where they received placebo per randomization allocation at study entry. Placebo was administered prior to infusional-5FU/leucovorin/bevacizumab at the same dose and schedule used during induction. Participants continued to receive treatment until disease progression, unacceptable toxicity, withdrawal of consent, discontinuation by Investigator, or the end of the trial, whichever occurred first. | |

| Reporting group values | Trilaciclib + FOLFOXIRI/Bevacizumab | Placebo + FOLFOXIRI/Bevacizumab | Total |
|--|-------------------------------------|---------------------------------|-------|
| Number of subjects | 164 | 162 | 326 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 120 | 124 | 244 |
| From 65-84 years | 44 | 38 | 82 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous Units: years | | | |
| arithmetic mean | 56.2 | 55.5 | - |
| standard deviation | ± 11.80 | ± 10.60 | - |
| Gender categorical Units: Subjects | | | |
| Female | 58 | 61 | 119 |
| Male | 106 | 101 | 207 |
| Race Units: Subjects | | | |
| White | 119 | 112 | 231 |
| Black or African American | 4 | 9 | 13 |
| Asian | 32 | 33 | 65 |
| Other | 3 | 0 | 3 |

| | | | |
|--------------|---|---|---|
| Not Reported | 3 | 3 | 6 |
| Unknown | 3 | 5 | 8 |

End points

End points reporting groups

| | |
|-----------------------|-------------------------------------|
| Reporting group title | Trilaciclib + FOLFOXIRI/Bevacizumab |
|-----------------------|-------------------------------------|

Reporting group description:

Participants received trilaciclib 240 milligram per meter square (mg/m²) on Days 1 and 2 administered intravenously (IV) prior to FOLFOXIRI (fluorouracil [5FU {infusional}], leucovorin, oxaliplatin, and irinotecan)/bevacizumab in 14-day cycles for up to 12 cycles (induction). Following completion of induction, participants continued in maintenance, where they received trilaciclib per randomization allocation at study entry. Trilaciclib was administered prior to infusional-5FU/leucovorin/bevacizumab at the same dose and schedule used during induction. Participants continued to receive treatment until disease progression, unacceptable toxicity, withdrawal of consent, discontinuation by Investigator, or the end of the trial, whichever occurred first.

| | |
|-----------------------|---------------------------------|
| Reporting group title | Placebo + FOLFOXIRI/Bevacizumab |
|-----------------------|---------------------------------|

Reporting group description:

Participants received placebo on Days 1 and 2 administered IV prior to FOLFOXIRI/bevacizumab in 14-day cycles for up to 12 cycles (induction). Following completion of induction, participants continued in maintenance, where they received placebo per randomization allocation at study entry. Placebo was administered prior to infusional-5FU/leucovorin/bevacizumab at the same dose and schedule used during induction. Participants continued to receive treatment until disease progression, unacceptable toxicity, withdrawal of consent, discontinuation by Investigator, or the end of the trial, whichever occurred first.

| | |
|----------------------------|-------------------------------------|
| Subject analysis set title | Trilaciclib + FOLFOXIRI/Bevacizumab |
|----------------------------|-------------------------------------|

| | |
|---------------------------|-----------------------------|
| Subject analysis set type | Modified intention-to-treat |
|---------------------------|-----------------------------|

Subject analysis set description:

Participants received trilaciclib 240 mg/m² on Days 1 and 2 administered IV prior to FOLFOXIRI/bevacizumab in 14-day cycles for up to 12 cycles (induction). Following completion of induction, participants continued in maintenance, where they received trilaciclib per randomization allocation at study entry. Trilaciclib was administered prior to infusional-5FU/leucovorin/bevacizumab at the same dose and schedule used during induction. Participants continued to receive treatment until disease progression, unacceptable toxicity, withdrawal of consent, discontinuation by Investigator, or the end of the trial, whichever occurred first.

| | |
|----------------------------|---------------------------------|
| Subject analysis set title | Placebo + FOLFOXIRI/Bevacizumab |
|----------------------------|---------------------------------|

| | |
|---------------------------|-----------------------------|
| Subject analysis set type | Modified intention-to-treat |
|---------------------------|-----------------------------|

Subject analysis set description:

Participants received placebo on Days 1 and 2 administered IV prior to FOLFOXIRI/bevacizumab in 14-day cycles for up to 12 cycles (induction). Following completion of induction, participants continued in maintenance, where they received placebo per randomization allocation at study entry. Placebo was administered prior to infusional-5FU/leucovorin/bevacizumab at the same dose and schedule used during induction. Participants continued to receive treatment until disease progression, unacceptable toxicity, withdrawal of consent, discontinuation by Investigator, or the end of the trial, whichever occurred first.

Primary: Duration Of Severe Neutropenia (DSN) (Grade 4) in Cycle 1 to Cycle 4

| | |
|-----------------|--|
| End point title | Duration Of Severe Neutropenia (DSN) (Grade 4) in Cycle 1 to Cycle 4 |
|-----------------|--|

End point description:

Severe Neutropenia was defined as Absolute neutrophil count(ANC) value<0.5 ×10⁹/Liter(L)(Grade 4 neutropenia per National Cancer Institute[NCI] Common Terminology Criteria for Adverse Events[CTCAE] criteria,version 5.0).DSN in Cycle 1-4 defined as number of days of first SN event that occurred in first 4 cycles of Induction.For participants with at least 1 SN event in Induction in Cycle 1,2,3 or 4,DSN was calculated for first occurrence of event following rules:For participants whose SN was resolved,DSN was derived as number of days from date of first SN occurrence to date of SN resolution;for participants who withdraw from study with unresolved neutropenia,DSN was derived as number of days from date of first SN occurrence to date of withdrawal.Modified intent-to-treat(mITT) analysis set:included all participants randomized in countries other than Ukraine and all participants in Ukraine who were randomized prior to 09-Sep-21,and who completed or completed Induction prior to

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

End point timeframe:

Cycle 1: Days 1, 2, 4, 6, 8, 10 and 12 and Cycles 2, 3, 4: Days 1 and 8 (each cycle is 14 days)

| End point values | Trilaciclib + FOLFOXIRI/Bevacizumab | Placebo + FOLFOXIRI/Bevacizumab | | |
|--------------------------------------|-------------------------------------|---------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 149 | 147 | | |
| Units: Days | | | | |
| arithmetic mean (standard deviation) | 0.1 (± 0.84) | 1.3 (± 3.14) | | |

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|---|
| Comparison groups | Trilaciclib + FOLFOXIRI/Bevacizumab v Placebo + FOLFOXIRI/Bevacizumab |
| Number of subjects included in analysis | 296 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 ^[1] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | -1.2 |
| Confidence interval | |
| level | Other: 96 % |
| sides | 2-sided |
| lower limit | -1.7 |
| upper limit | -0.6 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.27 |

Notes:

[1] - Two-sided p-value for treatment effect was generated from a nonparametric ANCOVA controlling for stratification factors of Region and Prior chemotherapy with study baseline ANC value as a covariate.

Primary: Number Of Participants With Occurrence Of SN During Induction

| | |
|-----------------|---|
| End point title | Number Of Participants With Occurrence Of SN During Induction |
|-----------------|---|

End point description:

Severe neutropenia was defined as an ANC value $< 0.5 \times 10^9/L$ (Grade 4 neutropenia per NCI CTCAE criteria, version 5.0). Occurrence of SN during Induction for a participant was defined as having as least one ANC value $< 0.5 \times 10^9/L$ among all ANC measurements during Induction regardless of scheduled or unscheduled visits. Analysis was performed on the mITT analysis set which included all participants randomized in countries other than Ukraine and all participants in Ukraine who were randomized prior to 09-Sep-21, and who completed or completed Induction prior to 24-Feb-22.

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

End point timeframe:

Cycle 1: Days 1, 2, 4, 6, 8, 10 and 12 and Cycles 2, 3, 4: Days 1 and 8 (each cycle is 14 days)

| End point values | Trilaciclib + FOLFOXIRI/Bevacizumab | Placebo + FOLFOXIRI/Bevacizumab | | |
|-----------------------------|-------------------------------------|---------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 149 | 147 | | |
| Units: Participants | 2 | 29 | | |

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|---|
| Comparison groups | Trilaciclib + FOLFOXIRI/Bevacizumab v Placebo + FOLFOXIRI/Bevacizumab |
| Number of subjects included in analysis | 296 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 ^[2] |
| Method | Modified Poisson model |
| Parameter estimate | Adjusted relative risk |
| Point estimate | 0.07 |
| Confidence interval | |
| level | Other: 96 % |
| sides | 2-sided |
| lower limit | 0.02 |
| upper limit | 0.31 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.051 |

Notes:

[2] - The aRR, its 96% CI, p-value were generated from modified Poisson model controlling for stratification factors of Region and Prior chemotherapy with baseline ANC value as a covariate. The log-transformed number of cycles was used as offset in model.

Secondary: Overall survival (OS)

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|---|-----------------------|
| End point title | Overall survival (OS) |
| End point description: | |
| OS was defined as the time (months) from the date of randomization to the date of death for participants who died in the study regardless of cause, or to the last contact date known to be alive for those who survived as of the date for final database lock (censored cases). 99999 indicates that median and upper limit of confidence interval (CI) was not estimable due to insufficient number of participants with events at study closure. mITT analysis set which included all participants randomized in countries other than Ukraine and all participants in Ukraine who were randomized prior to 09-Sep-21, and who completed or completed Induction prior to 24-Feb-22 | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 26 months | |

| End point values | Trilaciclib + FOLFOXIRI/Bev acizumab | Placebo + FOLFOXIRI/Bev acizumab | | |
|----------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 149 | 147 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 (day of first dose of any study drug) until 30 days after the last dose of study drug, approximately up to 115 weeks

Adverse event reporting additional description:

Analysis was performed on the Safety analysis set which included all randomized participants who received at least one dose of any study drug.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 24.1 |
|--------------------|------|

Reporting groups

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|-----------------------|-------------------------------------|
| Reporting group title | Trilaciclib + FOLFOXIRI/Bevacizumab |
|-----------------------|-------------------------------------|

Reporting group description:

Participants received trilaciclib 240 mg/m² on Days 1 and 2 administered IV prior to FOLFOXIRI/bevacizumab in 14-day cycles for up to 12 cycles (induction). Following completion of induction, participants continued in maintenance, where they received trilaciclib per randomization allocation at study entry. Trilaciclib was administered prior to infusional-5FU/leucovorin/bevacizumab at the same dose and schedule used during induction. Participants continued to receive treatment until disease progression, unacceptable toxicity, withdrawal of consent, discontinuation by Investigator, or the end of the trial, whichever occurred first.

| | |
|-----------------------|---------------------------------|
| Reporting group title | Placebo + FOLFOXIRI/Bevacizumab |
|-----------------------|---------------------------------|

Reporting group description:

Participants received placebo on Days 1 and 2 administered IV prior to FOLFOXIRI/bevacizumab in 14-day cycles for up to 12 cycles (induction). Following completion of induction, participants continued in maintenance, where they received placebo per randomization allocation at study entry. Placebo was administered prior to infusional-5FU/leucovorin/bevacizumab at the same dose and schedule used during induction. Participants continued to receive treatment until disease progression, unacceptable toxicity, withdrawal of consent, discontinuation by Investigator, or the end of the trial, whichever occurred first.

| Serious adverse events | Trilaciclib + FOLFOXIRI/Bevacizumab | Placebo + FOLFOXIRI/Bevacizumab | |
|---|-------------------------------------|---------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 47 / 159 (29.56%) | 47 / 160 (29.38%) | |
| number of deaths (all causes) | 8 | 3 | |
| number of deaths resulting from adverse events | 1 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Gastrointestinal carcinoma | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Hypertension | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 159 (0.63%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Venous thrombosis | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 2 / 160 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic embolus | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Embolism | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jugular vein thrombosis | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Superior vena cava syndrome | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombosis | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 3 / 160 (1.88%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Device related thrombosis | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 4 / 159 (2.52%) | 4 / 160 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 5 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 2 / 160 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Respiratory failure | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 159 (1.26%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary thrombosis | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Completed suicide | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 2 / 160 (1.25%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Drain site complication | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial injury | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Syncope | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 159 (0.63%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar radiculopathy | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myoclonic epilepsy | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 1 / 160 (0.63%) | |
| 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 | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 5 / 160 (3.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 5 / 160 (3.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anaemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 159 (0.00%) | 2 / 160 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 4 / 159 (2.52%) | 3 / 160 (1.88%) | |
| occurrences causally related to treatment / all | 0 / 5 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 159 (1.26%) | 3 / 160 (1.88%) | |
| occurrences causally related to treatment / all | 0 / 2 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 3 / 159 (1.89%) | 2 / 160 (1.25%) | |
| occurrences causally related to treatment / all | 3 / 4 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 3 / 160 (1.88%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 2 / 159 (1.26%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal obstruction | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 159 (0.63%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Intestinal perforation | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 2 / 159 (1.26%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal adhesions | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal fistula | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocutaneous fistula | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus paralytic | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestinal obstruction | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine perforation | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal rupture | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal perforation | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subileus | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 1 / 160 (0.63%) | |
| 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 | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myopathy | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Pneumonia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 3 / 159 (1.89%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 3 / 160 (1.88%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COVID-19 | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 2 / 160 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal abscess | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abscess limb | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal abscess | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anorectal infection | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 159 (0.00%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infectious pleural effusion | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal sepsis | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pelvic abscess | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hypokalaemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 159 (0.63%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Trilaciclib + FOLFOXIRI/Bevacizumab | Placebo + FOLFOXIRI/Bevacizumab | |
|---|--|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 155 / 159 (97.48%) | 159 / 160 (99.38%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 34 / 159 (21.38%) | 35 / 160 (21.88%) | |
| occurrences (all) | 82 | 86 | |
| Hypotension | | | |
| subjects affected / exposed | 5 / 159 (3.14%) | 8 / 160 (5.00%) | |
| occurrences (all) | 8 | 8 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 53 / 159 (33.33%) | 52 / 160 (32.50%) | |
| occurrences (all) | 136 | 136 | |
| Asthenia | | | |
| subjects affected / exposed | 28 / 159 (17.61%) | 28 / 160 (17.50%) | |
| occurrences (all) | 58 | 91 | |
| Pyrexia | | | |
| subjects affected / exposed | 17 / 159 (10.69%) | 22 / 160 (13.75%) | |
| occurrences (all) | 27 | 30 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 17 / 159 (10.69%) | 18 / 160 (11.25%) | |
| occurrences (all) | 20 | 31 | |
| Temperature intolerance | | | |
| subjects affected / exposed | 10 / 159 (6.29%) | 5 / 160 (3.13%) | |
| occurrences (all) | 14 | 6 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Epistaxis | | | |
| subjects affected / exposed | 7 / 159 (4.40%) | 28 / 160 (17.50%) | |
| occurrences (all) | 12 | 43 | |
| Cough | | | |
| subjects affected / exposed | 13 / 159 (8.18%) | 12 / 160 (7.50%) | |
| occurrences (all) | 16 | 17 | |
| Hiccups | | | |

| | | | |
|--------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed | 14 / 159 (8.81%) | 9 / 160 (5.63%) | |
| occurrences (all) | 17 | 12 | |
| Dyspnoea | | | |
| subjects affected / exposed | 11 / 159 (6.92%) | 8 / 160 (5.00%) | |
| occurrences (all) | 18 | 10 | |
| Nasal congestion | | | |
| subjects affected / exposed | 10 / 159 (6.29%) | 6 / 160 (3.75%) | |
| occurrences (all) | 10 | 6 | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 4 / 159 (2.52%) | 10 / 160 (6.25%) | |
| occurrences (all) | 5 | 14 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 5 / 159 (3.14%) | 8 / 160 (5.00%) | |
| occurrences (all) | 6 | 8 | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 15 / 159 (9.43%) | 15 / 160 (9.38%) | |
| occurrences (all) | 18 | 18 | |
| Anxiety | | | |
| subjects affected / exposed | 13 / 159 (8.18%) | 12 / 160 (7.50%) | |
| occurrences (all) | 16 | 13 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 20 / 159 (12.58%) | 24 / 160 (15.00%) | |
| occurrences (all) | 32 | 40 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 20 / 159 (12.58%) | 24 / 160 (15.00%) | |
| occurrences (all) | 42 | 41 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 12 / 159 (7.55%) | 15 / 160 (9.38%) | |
| occurrences (all) | 31 | 32 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 13 / 159 (8.18%) | 11 / 160 (6.88%) | |
| occurrences (all) | 19 | 18 | |
| White blood cell count decreased | | | |

| | | | |
|-------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed | 8 / 159 (5.03%) | 12 / 160 (7.50%) | |
| occurrences (all) | 20 | 36 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 9 / 159 (5.66%) | 9 / 160 (5.63%) | |
| occurrences (all) | 16 | 22 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 9 / 159 (5.66%) | 7 / 160 (4.38%) | |
| occurrences (all) | 22 | 11 | |
| Weight decreased | | | |
| subjects affected / exposed | 20 / 159 (12.58%) | 29 / 160 (18.13%) | |
| occurrences (all) | 27 | 42 | |
| Nervous system disorders | | | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 37 / 159 (23.27%) | 34 / 160 (21.25%) | |
| occurrences (all) | 67 | 53 | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 36 / 159 (22.64%) | 26 / 160 (16.25%) | |
| occurrences (all) | 81 | 89 | |
| Headache | | | |
| subjects affected / exposed | 32 / 159 (20.13%) | 26 / 160 (16.25%) | |
| occurrences (all) | 52 | 55 | |
| Paraesthesia | | | |
| subjects affected / exposed | 20 / 159 (12.58%) | 15 / 160 (9.38%) | |
| occurrences (all) | 29 | 22 | |
| Dizziness | | | |
| subjects affected / exposed | 13 / 159 (8.18%) | 19 / 160 (11.88%) | |
| occurrences (all) | 17 | 24 | |
| Neurotoxicity | | | |
| subjects affected / exposed | 10 / 159 (6.29%) | 13 / 160 (8.13%) | |
| occurrences (all) | 21 | 36 | |
| Dysgeusia | | | |
| subjects affected / exposed | 12 / 159 (7.55%) | 10 / 160 (6.25%) | |
| occurrences (all) | 17 | 11 | |
| Tremor | | | |

| | | | |
|--|----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 8 / 159 (5.03%) 9 | 1 / 160 (0.63%) 1 | |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 61 / 159 (38.36%) | 92 / 160 (57.50%) | |
| occurrences (all) | 212 | 293 | |
| Anaemia | | | |
| subjects affected / exposed | 57 / 159 (35.85%) | 61 / 160 (38.13%) | |
| occurrences (all) | 164 | 222 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 34 / 159 (21.38%) | 36 / 160 (22.50%) | |
| occurrences (all) | 106 | 85 | |
| Leukopenia | | | |
| subjects affected / exposed | 27 / 159 (16.98%) | 35 / 160 (21.88%) | |
| occurrences (all) | 109 | 129 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 83 / 159 (52.20%) | 118 / 160 (73.75%) | |
| occurrences (all) | 212 | 306 | |
| Nausea | | | |
| subjects affected / exposed | 85 / 159 (53.46%) | 101 / 160 (63.13%) | |
| occurrences (all) | 260 | 253 | |
| Vomiting | | | |
| subjects affected / exposed | 54 / 159 (33.96%) | 64 / 160 (40.00%) | |
| occurrences (all) | 118 | 139 | |
| Abdominal pain | | | |
| subjects affected / exposed | 34 / 159 (21.38%) | 36 / 160 (22.50%) | |
| occurrences (all) | 45 | 61 | |
| Constipation | | | |
| subjects affected / exposed | 38 / 159 (23.90%) | 29 / 160 (18.13%) | |
| occurrences (all) | 53 | 45 | |
| Stomatitis | | | |
| subjects affected / exposed | 25 / 159 (15.72%) | 42 / 160 (26.25%) | |
| occurrences (all) | 36 | 69 | |
| Dyspepsia | | | |

| | | | |
|---|-------------------|-------------------|--|
| subjects affected / exposed | 11 / 159 (6.92%) | 10 / 160 (6.25%) | |
| occurrences (all) | 14 | 10 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 9 / 159 (5.66%) | 8 / 160 (5.00%) | |
| occurrences (all) | 10 | 9 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 10 / 159 (6.29%) | 6 / 160 (3.75%) | |
| occurrences (all) | 18 | 8 | |
| Haemorrhoids | | | |
| subjects affected / exposed | 5 / 159 (3.14%) | 11 / 160 (6.88%) | |
| occurrences (all) | 5 | 14 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 7 / 159 (4.40%) | 9 / 160 (5.63%) | |
| occurrences (all) | 7 | 10 | |
| Abdominal distension | | | |
| subjects affected / exposed | 9 / 159 (5.66%) | 6 / 160 (3.75%) | |
| occurrences (all) | 10 | 8 | |
| Oral dysaesthesia | | | |
| subjects affected / exposed | 5 / 159 (3.14%) | 8 / 160 (5.00%) | |
| occurrences (all) | 10 | 18 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 23 / 159 (14.47%) | 25 / 160 (15.63%) | |
| occurrences (all) | 25 | 29 | |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 4 / 159 (2.52%) | 8 / 160 (5.00%) | |
| occurrences (all) | 11 | 23 | |
| Renal and urinary disorders | | | |
| Proteinuria | | | |
| subjects affected / exposed | 19 / 159 (11.95%) | 25 / 160 (15.63%) | |
| occurrences (all) | 47 | 49 | |
| Musculoskeletal and connective tissue disorders | | | |
| Muscle spasms | | | |
| subjects affected / exposed | 20 / 159 (12.58%) | 9 / 160 (5.63%) | |
| occurrences (all) | 31 | 12 | |
| Arthralgia | | | |

| | | | |
|--|-------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 9 / 159 (5.66%) 11 | 13 / 160 (8.13%) 23 | |
| Back pain subjects affected / exposed occurrences (all) | 9 / 159 (5.66%) 12 | 11 / 160 (6.88%) 19 | |
| Pain in extremity subjects affected / exposed occurrences (all) | 8 / 159 (5.03%) 9 | 6 / 160 (3.75%) 9 | |
| Infections and infestations COVID-19 subjects affected / exposed occurrences (all) | 18 / 159 (11.32%) 18 | 22 / 160 (13.75%) 24 | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 11 / 159 (6.92%) 20 | 10 / 160 (6.25%) 11 | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 7 / 159 (4.40%) 8 | 12 / 160 (7.50%) 13 | |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 36 / 159 (22.64%) 44 | 39 / 160 (24.38%) 71 | |
| Hypokalaemia subjects affected / exposed occurrences (all) | 21 / 159 (13.21%) 44 | 21 / 160 (13.13%) 33 | |
| Dehydration subjects affected / exposed occurrences (all) | 12 / 159 (7.55%) 12 | 11 / 160 (6.88%) 18 | |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 11 / 159 (6.92%) 15 | 8 / 160 (5.00%) 14 | |
| Hypophosphataemia subjects affected / exposed occurrences (all) | 6 / 159 (3.77%) 9 | 12 / 160 (7.50%) 21 | |
| Hypoalbuminaemia | | | |

| | | | |
|-----------------------------|-----------------|------------------|--|
| subjects affected / exposed | 6 / 159 (3.77%) | 11 / 160 (6.88%) | |
| occurrences (all) | 13 | 18 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 9 / 159 (5.66%) | 3 / 160 (1.88%) | |
| occurrences (all) | 12 | 4 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 11 January 2021 | China was added to the study and to the list of countries for stratification. Regions include United States, Eastern Europe, Western Europe, and China. An exclusion criterion (#15) was added to exclude those with chronic inflammatory bowel disease and/or intestinal obstruction. It was noted that participants should not be treated until the obstruction has resolved. An exclusion criterion (#19) was added to specify that participants requiring ongoing or anticipated treatment with potent CYP450 3A4 inhibitors or inducers should not be included. An exclusion criterion (#20) was added to prohibit the inclusion of participants with ongoing or anticipated treatment with sorivudine or brivudine. Exclusion criterion # 28 was added to specify any contraindications to the administration of FOLFOXIRI and bevacizumab at the discretion of the investigator. Language was added to clarify that the strata information entered in Interactive web response system (IWRS) at the time of randomization would be used for all stratified statistical analyses. |
| 07 July 2021 | Text was added to the criteria for starting Cycle 2 in Section 9.4 to clarify the guidance for initiating subsequent treatment cycles. In addition, the dose modification guidelines for Grade 2 peripheral sensory neuropathy were updated in Table 9 to accommodate differences in clinical practice. |
| 30 August 2022 | The sample size was adjusted from 296 to 326 to mitigate the impact of the Russian-Ukraine war on data integrity and to ensure that the objectives of PRESERVE-1 would not be compromised. An additional 30 participants were randomized from outside Ukraine. To account for data integrity issues resulting from the war in Ukraine, a modified intent-to-treat (mITT) population would be utilized as the primary analysis population for all efficacy evaluations. The criteria for the mITT were included in the protocol. The primary myelosuppression endpoint was updated to duration of severe neutropenia (DSN) from Cycles 1 to 4. Measuring DSN during the timeframe of occurrence of the majority of severe neutropenia events, ie, Cycles 1 through 4 allowed an assessment of the risk of febrile neutropenia during the time of greatest clinical risk to participants. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported