# Clinical trial results:
# An open-label, randomised, phase III study comparing trifluridine/tipiracil in combination with bevacizumab to trifluridine/tipiracil monotherapy in patients with refractory metastatic colorectal cancer (SUNLIGHT study)

## Summary

| | |
|---|---|
| EudraCT number | 2020-001976-14 |
| Trial protocol | DK FR DE HU BE AT IT |
| Global end of trial date | 12 September 2023 |

**Results information**

| | |
|---|---|
| Result version number | v2 |
| This version publication date | 17 April 2024 |
| First version publication date | 28 July 2023 |
| Version creation reason | • New data added to full data set<br>Safety data are being updated based on all data collected from study start up to study completion. Efficacy results are the same as those that were reported in the results v1 at primary completion date. |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | CL3-95005-007 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04737187 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Investigational New Drug Number: 57674 |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | I.R.I.S. |
| Sponsor organisation address | 50 rue Carnot, Suresnes Cedex, France, 92284 |
| Public contact | Clinical Studies Department, Institut de Recherches Internationales Servier, +33 155 72 43 66, clinicaltrials@servier.com |
| Scientific contact | Clinical Studies Department, Institut de Recherches Internationales Servier, +33 155 72 43 66, clinicaltrials@servier.com |
| Sponsor organisation name | Taiho Oncology, Inc. |
| Sponsor organisation address | 101 Carnegie Center, Suite 101 Princeton, New Jersey, Princeton, United States, 08540 |
| Public contact | clinicaltrialinfo@taihooncology.com, Taiho Oncology, Inc., 1-609 250-7336, clinicaltrialinfo@taihooncology.com |
| Scientific contact | clinicaltrialinfo@taihooncology.com, Taiho Oncology, Inc., 1-609 250-7336, clinicaltrialinfo@taihooncology.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 | 12 September 2023 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 19 July 2022 |
| Global end of trial reached? | Yes |
| Global end of trial date | 12 September 2023 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To demonstrate the superiority of trifluridine/tipiracil in combination with bevacizumab over trifluridine/tipiracil monotherapy in terms of Overall Survival (OS) in patients with refractory metastatic colorectal cancer (mCRC).

Protection of trial subjects:

The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki, 1964, as revised in 2013, as revised in Fortaleza, 2013 with the GCP and with the applicable regulatory requirements. All the patients were to freely give their written informed consent before their selection in the study.

Background therapy:

-

Evidence for comparator:

Trifluridine/tipiracil as control arm

| | |
|---|---|
| Actual start date of recruitment | 25 November 2020 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Poland: 34 |
| Country: Number of subjects enrolled | Spain: 115 |
| Country: Number of subjects enrolled | Austria: 15 |
| Country: Number of subjects enrolled | Belgium: 7 |
| Country: Number of subjects enrolled | Denmark: 20 |
| Country: Number of subjects enrolled | France: 28 |

| | |
|---|---|
| Country: Number of subjects enrolled | Germany: 10 |
| Country: Number of subjects enrolled | Hungary: 47 |
| Country: Number of subjects enrolled | Italy: 39 |
| Country: Number of subjects enrolled | Russian Federation: 77 |
| Country: Number of subjects enrolled | Brazil: 63 |
| Country: Number of subjects enrolled | Ukraine: 21 |
| Country: Number of subjects enrolled | United States: 16 |
| Worldwide total number of subjects | 492 |
| EEA total number of subjects | 315 |

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) | 275 |
| From 65 to 84 years | 216 |
| 85 years and over | 1 |

## Subject disposition

### Recruitment

Recruitment details:

Investigators were oncologists.

### Pre-assignment

Screening details:

Patients with histologically confirmed, unresectable adenocarcinoma of the colon or rectum were eligible for participation if they had received no more than two previous chemotherapy regimens for the treatment of advanced colorectal cancer and had had progressive disease or if their last regimen had caused unacceptable adverse effects.

### Period 1

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

Blinding implementation details:

This was an open-label study, no IMP blinding was required.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | FTD/TPI plus Bev |

Arm description:

Subjects received trifluridine/tipiracil (FTD/TPI) in combination with bevacizumab (Bev)

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Trifluridine/Tipiracil (FTD/TPI) |
| Investigational medicinal product code | S95005 |
| Other name | TAS-102; Lonsurf® |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

FTD/TPI + Bevacizumab
FTD/TPI (35 mg/m²/dose) was administered orally twice a day (BID), within 1 hour after completion of morning and evening meals, 5 days on/2 days off, over 2 weeks, followed by a 14-day rest; with bevacizumab (5 mg/kg, intravenous [IV]) administered every 2 weeks (Day 1 and Day 15). This treatment cycle was repeated every 4 weeks.

| | |
|---|---|
| Investigational medicinal product name | Bevacizumab |
| Investigational medicinal product code | |
| Other name | Avastin® |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

FTD/TPI + Bevacizumab
FTD/TPI (35 mg/m²/dose) was administered orally twice a day (BID), within 1 hour after completion of morning and evening meals, 5 days on/2 days off, over 2 weeks, followed by a 14-day rest; with bevacizumab (5 mg/kg, intravenous [IV]) administered every 2 weeks (Day 1 and Day 15). This treatment cycle was repeated every 4 weeks.

| | |
|---|---|
| **Arm title** | FTD/TPI |

Arm description:

Subjects received trifluridine/tipiracil (FTD/TPI) as monotherapy

| | |
|---|---|
| Arm type | Active comparator |

| | |
|---|---|
| Investigational medicinal product name | Trifluridine/Tipiracil (FTD/TPI) |
| Investigational medicinal product code | S95005 |
| Other name | TAS-102; Lonsurf® |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

FTD/TPI as monotherapy
FTD/TPI (35 mg/m²/dose) was administered orally BID, within 1 hour after completion of morning and evening meals, 5 days on/2 days off, over 2 weeks, followed by a 14-day rest. This treatment cycle was repeated every 4 weeks.

| **Number of subjects in period 1** | FTD/TPI plus Bev | FTD/TPI |
|---|---|---|
| Started | 246 | 246 |
| Completed | 246 | 246 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | FTD/TPI plus Bev |
| Reporting group description: | |
| Subjects received trifluridine/tipiracil (FTD/TPI) in combination with bevacizumab (Bev) | |
| Reporting group title | FTD/TPI |
| Reporting group description: | |
| Subjects received trifluridine/tipiracil (FTD/TPI) as monotherapy | |

| Reporting group values | FTD/TPI plus Bev | FTD/TPI | Total |
|---|---|---|---|
| Number of subjects | 246 | 246 | 492 |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 146 | 129 | 275 |
| From 65-84 years | 100 | 116 | 216 |
| 85 years and over | 0 | 1 | 1 |
| Age continuous<br>Units: years | | | |
| median | 62.00 | 64.00 | |
| full range (min-max) | 20.0 to 84.0 | 24.0 to 90.0 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 124 | 112 | 236 |
| Male | 122 | 134 | 256 |

| Subject analysis sets | |
|---|---|
| Subject analysis set title | Full Analysis Set |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Full Analysis Set (FAS): based on the intention-to-treat principle, all patients to whom a therapeutic unit was randomly assigned using Interactive Web Response System (IWRS). Patients were analysed in the arm they were assigned by randomisation. | |

| | |
|---|---|
| Subject analysis set title | Safety Set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| All patients having taken at least one dose of FTD/TPI. Patients were analysed according to the treatment actually received. | |

| Reporting group values | Full Analysis Set | Safety Set | |
|---|---|---|---|
| Number of subjects | 492 | 492 | |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 275 | 275 | |
| From 65-84 years | 216 | 216 | |
| 85 years and over | 1 | 1 | |

| | | | |
|---|---|---|---|
| Age continuous<br>Units: years | | | |
| median | 63.00 | 63.00 | |
| full range (min-max) | 20.0 to 90.0 | 20.0 to 90.0 | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 236 | 236 | |
| Male | 256 | 256 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | FTD/TPI plus Bev |
| Reporting group description: | |
| Subjects received trifluridine/tipiracil (FTD/TPI) in combination with bevacizumab (Bev) | |
| Reporting group title | FTD/TPI |
| Reporting group description: | |
| Subjects received trifluridine/tipiracil (FTD/TPI) as monotherapy | |
| Subject analysis set title | Full Analysis Set |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Full Analysis Set (FAS): based on the intention-to-treat principle, all patients to whom a therapeutic unit was randomly assigned using Interactive Web Response System (IWRS). Patients were analysed in the arm they were assigned by randomisation. | |

| | |
|---|---|
| Subject analysis set title | Safety Set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| All patients having taken at least one dose of FTD/TPI. Patients were analysed according to the treatment actually received. | |

### Primary: Overall survival

| | |
|---|---|
| End point title | Overall survival |
| End point description: | |
| The primary estimand of interest was defined to assess the effect of the randomised treatments on the survival duration in all patients regardless of whether or not intercurrent events had occurred (treatment policy strategy). | |

| | |
|---|---|
| End point type | Primary |
| End point timeframe: | |
| Overall survival (OS) was defined as the observed time elapsed between the date of randomisation and the date of death due to any cause. | |

| End point values | FTD/TPI plus Bev | FTD/TPI | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 246 | 246 | | |
| Units: month | | | | |
| number (confidence interval 95%) | | | | |
| Survival Median (months) | 10.78 (9.36 to 11.83) | 7.46 (6.34 to 8.57) | | |
| Survival probability at 6 months | 0.77 (0.72 to 0.82) | 0.61 (0.55 to 0.67) | | |
| Survival probability at 12 months | 0.43 (0.36 to 0.49) | 0.30 (0.24 to 0.36) | | |
| Survival probability at 18 months | 0.28 (0.19 to 0.37) | 0.15 (0.09 to 0.22) | | |

## Statistical analyses

| **Statistical analysis title** | Statistical analysis |
|---|---|

Statistical analysis description:

The primary estimand was defined to assess the effect of the randomised treatments on the survival duration in all patients regardless of whether or not intercurrent events had occurred (treatment policy strategy).

| | |
|---|---|
| Comparison groups | FTD/TPI plus Bev v FTD/TPI |
| Number of subjects included in analysis | 492 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 [1] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.61 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.49 |
| upper limit | 0.77 |

Notes:

[1] - One-sided p < 0.001, stratified log-rank test, with a target p-value < 0.025 for level of significance.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All adverse events that occurred or worsened or became serious between the first IMP intake and the last IMP intake+30 days (both included).

Adverse event reporting additional description:

Number of events for each treatment arm were provided for Serious Adverse Events over the study period and Emergent Adverse Events on treatment period.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 25.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | FTD/TPI |

Reporting group description:

Subjects received trifluridine/tipiracil (FTD/TPI) as monotherapy

| | |
|---|---|
| Reporting group title | FTD/TPI plus Bev |

Reporting group description:

Subjects received trifluridine/tipiracil (FTD/TPI) in combination with bevacizumab (Bev)

| Serious adverse events | FTD/TPI | FTD/TPI plus Bev | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 79 / 246 (32.11%) | 66 / 246 (26.83%) | |
| number of deaths (all causes) | 224 | 208 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 11 / 246 (4.47%) | 6 / 246 (2.44%) | |
| occurrences causally related to treatment / all | 0 / 11 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 11 | 0 / 6 | |
| Metastases to meninges | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to spine | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Tumour pain | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to central nervous system | | | |
| subjects affected / exposed | 4 / 246 (1.63%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cancer pain | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant pleural effusion | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to ovary | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 246 (0.00%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 3 / 246 (1.22%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 2 / 246 (0.81%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 246 (0.81%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Malaise | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (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 | | | |
| Anaphylactic reaction | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Prostatitis | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| 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 / 246 (1.63%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 4 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea at rest | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (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 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychomotor retardation | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| C-reactive protein increased | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal stoma output decreased | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutrophil count increased | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Neutrophil count decreased | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Stoma site haemorrhage | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal stoma complication | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Phimosis | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 246 (0.41%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericarditis | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Nervous system disorders | | | |
| Balance disorder | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhagic stroke | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Diplegia | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic encephalopathy | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Blood and lymphatic system disorders** | | | |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anaemia | | | |
| subjects affected / exposed | 9 / 246 (3.66%) | 3 / 246 (1.22%) | |
| occurrences causally related to treatment / all | 7 / 9 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 6 / 246 (2.44%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 6 / 6 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal lymphadenopathy | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Glaucoma | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 5 / 246 (2.03%) | 9 / 246 (3.66%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 12 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Vomiting | | | |
| subjects affected / exposed | 2 / 246 (0.81%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 1 / 2 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestinal obstruction | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 246 (0.00%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 2 / 246 (0.81%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites | | | |
| subjects affected / exposed | 2 / 246 (0.81%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subileus | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Abdominal hernia | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal tenderness | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| 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 | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal fistula | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal perforation | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal perforation | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestinal stenosis | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic colitis | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 246 (1.22%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 2 / 246 (0.81%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis haemorrhagic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal ischaemia | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal stenosis | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal stenosis | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Faecaloma | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mechanical ileus | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Jaundice cholestatic | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 3 / 246 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jaundice | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 5 / 246 (2.03%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cholangitis | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bile duct stenosis | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Biliary dilatation | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bile duct stone | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| 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 | 5 / 246 (2.03%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 1 | |
| Cholestasis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatomegaly | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 2 / 246 (0.81%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelocaliectasis | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary incontinence | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prerenal failure | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Arthralgia | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (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 | | | |
| COVID-19 | | | |
| subjects affected / exposed | 6 / 246 (2.44%) | 5 / 246 (2.03%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Septic shock | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 246 (0.81%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection pseudomonal | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular device infection | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal sepsis | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Intestinal sepsis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paracancerous pneumonia | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia streptococcal | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postoperative abscess | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection bacterial | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacterial pyelonephritis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 246 (0.81%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 2 / 246 (0.81%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal infection | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacterial prostatitis | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Klebsiella sepsis | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pelvic abscess | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (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 | 1 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 2 / 246 (0.81%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypernatraemia | | | |
| subjects affected / exposed | 0 / 246 (0.00%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cachexia | | | |
| subjects affected / exposed | 2 / 246 (0.81%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 246 (0.41%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | FTD/TPI | FTD/TPI plus Bev | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 237 / 246 (96.34%) | 238 / 246 (96.75%) | |
| Investigations | | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 18 / 246 (7.32%) | 34 / 246 (13.82%) | |
| occurrences (all) | 27 | 114 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 6 / 246 (2.44%) | 24 / 246 (9.76%) | |
| occurrences (all) | 7 | 42 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 14 / 246 (5.69%) | 20 / 246 (8.13%) | |
| occurrences (all) | 16 | 22 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 14 / 246 (5.69%) | 20 / 246 (8.13%) | |
| occurrences (all) | 16 | 21 | |
| Weight decreased | | | |
| subjects affected / exposed | 12 / 246 (4.88%) | 23 / 246 (9.35%) | |
| occurrences (all) | 13 | 24 | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 14 / 246 (5.69%) | 14 / 246 (5.69%) | |
| occurrences (all) | 15 | 16 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 5 / 246 (2.03%) | 25 / 246 (10.16%) | |
| occurrences (all) | 5 | 28 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 9 / 246 (3.66%) | 20 / 246 (8.13%) | |
| occurrences (all) | 13 | 36 | |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 126 / 246 (51.22%) | 153 / 246 (62.20%) | |
| occurrences (all) | 275 | 560 | |
| Anaemia | | | |
| subjects affected / exposed | 72 / 246 (29.27%) | 77 / 246 (31.30%) | |
| occurrences (all) | 81 | 102 | |

| | | | |
|---|---|---|---|
| Thrombocytopenia | | | |
| subjects affected / exposed | 29 / 246 (11.79%) | 44 / 246 (17.89%) | |
| occurrences (all) | 35 | 123 | |
| Leukopenia | | | |
| subjects affected / exposed | 21 / 246 (8.54%) | 19 / 246 (7.72%) | |
| occurrences (all) | 42 | 43 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 58 / 246 (23.58%) | 60 / 246 (24.39%) | |
| occurrences (all) | 68 | 98 | |
| Fatigue | | | |
| subjects affected / exposed | 38 / 246 (15.45%) | 54 / 246 (21.95%) | |
| occurrences (all) | 46 | 70 | |
| Pyrexia | | | |
| subjects affected / exposed | 13 / 246 (5.28%) | 15 / 246 (6.10%) | |
| occurrences (all) | 13 | 20 | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 69 / 246 (28.05%) | 94 / 246 (38.21%) | |
| occurrences (all) | 97 | 214 | |
| Diarrhoea | | | |
| subjects affected / exposed | 47 / 246 (19.11%) | 54 / 246 (21.95%) | |
| occurrences (all) | 69 | 127 | |
| Vomiting | | | |
| subjects affected / exposed | 35 / 246 (14.23%) | 50 / 246 (20.33%) | |
| occurrences (all) | 42 | 108 | |
| Abdominal pain | | | |
| subjects affected / exposed | 26 / 246 (10.57%) | 29 / 246 (11.79%) | |
| occurrences (all) | 27 | 44 | |
| Constipation | | | |
| subjects affected / exposed | 27 / 246 (10.98%) | 28 / 246 (11.38%) | |
| occurrences (all) | 34 | 45 | |
| Stomatitis | | | |
| subjects affected / exposed | 10 / 246 (4.07%) | 29 / 246 (11.79%) | |
| occurrences (all) | 10 | 45 | |
| Abdominal pain upper | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 9 / 246 (3.66%) | 22 / 246 (8.94%) | |
| occurrences (all) | 10 | 34 | |
| Renal and urinary disorders | | | |
| Proteinuria | | | |
| subjects affected / exposed | 4 / 246 (1.63%) | 15 / 246 (6.10%) | |
| occurrences (all) | 4 | 21 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 5 / 246 (2.03%) | 18 / 246 (7.32%) | |
| occurrences (all) | 6 | 19 | |
| Back pain | | | |
| subjects affected / exposed | 13 / 246 (5.28%) | 19 / 246 (7.72%) | |
| occurrences (all) | 16 | 20 | |
| Infections and infestations | | | |
| COVID-19 | | | |
| subjects affected / exposed | 4 / 246 (1.63%) | 19 / 246 (7.72%) | |
| occurrences (all) | 5 | 19 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 39 / 246 (15.85%) | 55 / 246 (22.36%) | |
| occurrences (all) | 45 | 67 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 30 December 2020 | Amendment No. 1, dated 30 December 2020 was applicable in all countries. It mainly concerned:<br>- New exclusion criteria for patients with uncontrolled hypertension, patients with history of any life-threatening VEGF related adverse event and patients with proteinuria.<br>- Sponsorship of TOI for the investigational sites in USA.<br>- Change of the time window to perform the tumour assessment.<br>- Baseline ECG obtained prior to patient having signed the ICF could be used if the date of ECG was within 28 days of randomisation.<br>- Clarifications were made. They concerned mainly:<br>*Inclusion criterion number 4: to clarify that the considered prior treatment regimens were those for advanced CRC setting.<br>* IMP management.<br>* Definition of the end of study.<br>* Reasons for discontinuation and restart of treatment period, in case of COVID-19 infection.<br>* Follow-up procedures in case of withdrawal of consent.<br>* Certification of the scales to be used during the study.<br>* Definition of overdose.<br>* Definition of Events requiring an immediate notification (ERIN).<br>* All fatal events occurring between ICF signature and IMP administration were to be reported on AE form.<br>* Precisions in statistical and safety parts of the protocol.<br>* Data sharing section.<br>- Modification of archiving patients' data from 15 to 25 years.<br>Addition of US Product Information in appendix of the study protocol.<br>- Inclusion of a local amendment issued for Italy, Denmark and Germany to specify that pregnancy tests were to be performed at each cycle during treatment period for female patients of childbearing potential.<br>- Inclusion of local amendment issued for France to specify that all patients in France should have received an anti-VEGF monoclonal antibody before entry in the study. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported