



Clinical trial results:

A Randomized, Phase 3 Study of Eryaspase in Combination with Chemotherapy versus Chemotherapy Alone as Second-Line Treatment in Patients with Pancreatic Adenocarcinoma

Summary

| | |
|--------------------------|----------------------------|
| EudraCT number | 2018-000572-15 |
| Trial protocol | FI SE ES AT DE NL DK BE IT |
| Global end of trial date | 18 January 2022 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 20 May 2023 |
| First version publication date | 20 May 2023 |

Trial information

Trial identification

| | |
|-----------------------|------------------|
| Sponsor protocol code | GRASPANC-2018-01 |
|-----------------------|------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03665441 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Erytech Pharma |
| Sponsor organisation address | Bioserra 60 Av Rockefeller, Lyon, France, 69008 |
| Public contact | Anu Gupta, ERYTECH Pharma, 1 7327424937, anu.gupta@erytech.com |
| Scientific contact | Iman El-Hariry, ERYTECH Pharma, 1 617 9592131, iman.elhariry@erytech.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 | 30 August 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 30 August 2021 |
| Global end of trial reached? | Yes |
| Global end of trial date | 18 January 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to determine whether the addition of eryaspase to chemotherapy improves overall survival (OS) in second-line treatment of pancreatic adenocarcinoma compared to chemotherapy alone.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

An independent data monitoring committee reviewed the interim results from the study as well as safety on a regular basis during the trial. The IDMC had the potential to stop the study in case of safety concerns or for lack of efficacy.

Background therapy:

Patients could receive one of 2 chemotherapy regimen, Gemcitabine and Abraxane or Irinotecan-based therapy. The choice of the chemotherapy regimen was determined by the prior treatment patient received in the first-line setting. Thus:

- If a patient received prior gemcitabine/Abraxane in the first-line setting, then on disease progression, the patient was assigned to FOLFIRI (or Onivyde/5-FU/LV) in the current study.
- If a patient received prior irinotecan-based therapy (FOLinic acid-Fluorouracil-IRinotecan-Oxaliplatin; FOLFIRINOX), then on disease progression, the patient was assigned to gemcitabine/Abraxane in the current study.
- If patient received neither, the chemotherapy was investigator chose one of the 2 regimen.

Evidence for comparator:

In the second-line setting, there remains a lack of consensus regarding the standard of care. Treatment options are dependent on the risk-benefit balance for the patient and the treatment received in the first line. In 2017, treatment guidelines were updated to recommend that the combination of nanoliposomal irinotecan (Onivyde®) with fluoropyrimidine regimens (i.e., 5-FU with LV) can be considered an active and tolerable treatment option in fit patients (ECOG PS less than 2) previously treated with gemcitabine-based therapy. This combination extended survival by 1.9 months compared with patients treated with 5-FU in combination with LV. No formal recommendations are available for patients who have progressed on first-line FOLFIRINOX; although gemcitabine is widely used in this setting.

| | |
|---|-------------------|
| Actual start date of recruitment | 01 September 2018 |
| 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 | Netherlands: 2 |
| Country: Number of subjects enrolled | Spain: 170 |
| Country: Number of subjects enrolled | Sweden: 3 |

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United Kingdom: 3 |
| Country: Number of subjects enrolled | Austria: 6 |
| Country: Number of subjects enrolled | Belgium: 25 |
| Country: Number of subjects enrolled | Czechia: 4 |
| Country: Number of subjects enrolled | Finland: 3 |
| Country: Number of subjects enrolled | France: 211 |
| Country: Number of subjects enrolled | Germany: 18 |
| Country: Number of subjects enrolled | Italy: 28 |
| Country: Number of subjects enrolled | United States: 39 |
| Worldwide total number of subjects | 512 |
| EEA total number of subjects | 470 |

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) | 282 |
| From 65 to 84 years | 229 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details:

A total of 512 patient were randomized 1:1 to receive eryaspase with chemotherapy or chemotherapy alone. Of these, 494 patients received treatment.

Pre-assignment

Screening details:

684 patients were screened to enroll 512 patients who met the eligibility criteria.

Key eligibility criteria included patients who were 18 years of age or older, had pancreatic adenocarcinoma, Stage III or IV disease, had failed 1 line of systemic therapy in advanced setting and had measurable disease per RECIST 1.1 and in good general health.

Period 1

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

Arms

| | |
|------------------------------|--------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Eryaspase + chemotherapy |

Arm description:

Patients randomized to Arm A receive eryaspase in combination with gemcitabine and Abraxane or irinotecan and 5-FU/LV.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | eryaspase |
| Investigational medicinal product code | |
| Other name | L-asparaginase encapsulated in RBCs, GRASPA, ERY001 |
| Pharmaceutical forms | Dispersion for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Eryaspase (100 U/kg) was administered every 2 weeks (Day 1 and Day 15 of 4 week cycle) in combination with standard chemotherapy, gemcitabine and Abraxane of irinotecan and 5-FU/LV. Prior to administration, an irregular antibody test and crossmatch test was completed. Eryaspase was administered until disease progression or intolerable toxicity or a patient discontinues treatment for other reasons.

| | |
|--|--------------------------|
| Investigational medicinal product name | Gemcitabine and Abraxane |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Gemcitabine and Abraxane were administered on Days 1, 8, and 15 of each 4-week cycle as follows:

- Abraxane: 125 mg/m² IV over 30-40 minutes, followed by
- Gemcitabine: 1000 mg/m² IV over 30 minutes.

| | |
|--|---|
| Investigational medicinal product name | Irinotecan (or Onivyde) and 5-flourouracil and Leucovorin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

FOLFIRI (irinotecan, 5-FU, and leucovorin) was administered every 2 weeks on Day 1 and Day 15 of each 4-week cycle as follows:

- Irinotecan 180 mg/m² IV infusion
- Leucovorin 400 mg/m² IV infusion over 2 hours,
- 5-FU 400 mg/m² IV bolus injection over 2-4 minutes, immediately following leucovorin infusion, and
- 5-FU 2400 mg/m² IV continuous infusion over 46 hours, immediately following bolus 5-FU

Or

Onivyde (irinotecan nanoliposomal) + 5-FU/leucovorin were administered on Days 1 and 15 of each 4-week cycle as follows:

- Onivyde 70 mg/m² IV over 90 minutes
- Leucovorin 400 mg/m² IV over 30 minutes, and
- 5-FU 2400 mg/m² over 46 hours

| | |
|------------------|--------------------|
| Arm title | Chemotherapy alone |
|------------------|--------------------|

Arm description:

Patients randomized to Arm B receive either gemcitabine and Abraxane or irinotecan and 5-FU/LV.

| | |
|--|--------------------------|
| Arm type | Standard of Care |
| Investigational medicinal product name | Gemcitabine and Abraxane |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Gemcitabine and Abraxane were administered on Days 1, 8, and 15 of each 4-week cycle as follows:

- Abraxane: 125 mg/m² IV over 30-40 minutes, followed by
- Gemcitabine: 1000 mg/m² IV over 30 minutes.

| | |
|--|---|
| Investigational medicinal product name | Irinotecan (or Onivyde) and 5-flourouracil and Leucovorin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

FOLFIRI (irinotecan, 5-FU, and leucovorin) was administered every 2 weeks on Day 1 and Day 15 of each 4-week cycle as follows:

- Irinotecan 180 mg/m² IV infusion
- Leucovorin 400 mg/m² IV infusion over 2 hours,
- 5-FU 400 mg/m² IV bolus injection over 2-4 minutes, immediately following leucovorin infusion, and
- 5-FU 2400 mg/m² IV continuous infusion over 46 hours, immediately following bolus 5-FU

Or

Onivyde (irinotecan nanoliposomal) + 5-FU/leucovorin were administered on Days 1 and 15 of each 4-week cycle as follows:

- Onivyde 70 mg/m² IV over 90 minutes
- Leucovorin 400 mg/m² IV over 30 minutes, and
- 5-FU 2400 mg/m² over 46 hours

| Number of subjects in period 1 | Eryaspase + chemotherapy | Chemotherapy alone |
|--------------------------------|--------------------------|--------------------|
| Started | 255 | 257 |
| Completed | 209 | 211 |
| Not completed | 46 | 46 |
| On treatment | 9 | 6 |
| Consent withdrawn by subject | 4 | 11 |
| Survival Follow up | 30 | 27 |
| Lost to follow-up | 3 | 2 |

Baseline characteristics

Reporting groups

| | |
|--|--------------------------|
| Reporting group title | Eryaspase + chemotherapy |
| Reporting group description: Patients randomized to Arm A receive eryaspase in combination with gemcitabine and Abraxane or irinotecan and 5-FU/LV. | |
| Reporting group title | Chemotherapy alone |
| Reporting group description: Patients randomized to Arm B receive either gemcitabine and Abraxane or irinotecan and 5-FU/LV. | |

| Reporting group values | Eryaspase + chemotherapy | Chemotherapy alone | Total |
|---|--------------------------|--------------------|-------|
| Number of subjects | 255 | 257 | 512 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 140 | 142 | 282 |
| Adults (65 years and older) | 115 | 115 | 230 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 121 | 124 | 245 |
| Male | 134 | 133 | 267 |
| Geographical Region | | | |
| Units: Subjects | | | |
| Europe | 236 | 237 | 473 |
| USA | 19 | 20 | 39 |
| ECOG | | | |
| Units: Subjects | | | |
| ECOG=0 | 107 | 105 | 212 |
| ECOG=1 | 148 | 152 | 300 |
| Time from initial diagnosis of advanced disease to randomization (months) | | | |
| Units: Subjects | | | |
| <6 months | 79 | 74 | 153 |
| >=6 months | 176 | 183 | 359 |
| Chemotherapy regimen in study | | | |
| Units: Subjects | | | |
| Gemcitabine and Abraxane | 148 | 148 | 296 |
| Irinotecan and 5-FU/LV | 107 | 109 | 216 |

Subject analysis sets

| | |
|--|-------------------------|
| Subject analysis set title | Final Analysis |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: The ITT population comprised all patients who were randomized to study treatment, regardless of whether they received study medication. | |
| Subject analysis set title | Final Analysis - Safety |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The safety population is defined as all patients who received at least one dose of study drug.

| | |
|----------------------------|-------------------------------|
| Subject analysis set title | Final Analysis - Per Protocol |
| Subject analysis set type | Per protocol |

Subject analysis set description:

The per protocol population is defined as a subset of ITT patients who receive at least one dose of study medication and had no major protocol deviation in inclusion/exclusion criteria.

| | |
|----------------------------|----------------------|
| Subject analysis set title | Final Analysis - PRO |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

The PRO population will consist of all patients who receive at least one dose of the study treatment and provide answers to at least some items of the EORTC QLQ-C30 at Cycle 1 Day 1 (i.e, baseline) and a time point after the date of first dose of study treatment.

| | |
|----------------------------|---------------------|
| Subject analysis set title | Final Analysis - PK |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

The pharmacokinetic analysis set will include all randomized patients who received at least one dose of eryaspase and who have at least one post-baseline PK assessment.

| Reporting group values | Final Analysis | Final Analysis - Safety | Final Analysis - Per Protocol |
|--|----------------|-------------------------|-------------------------------|
| Number of subjects | 512 | 494 | 491 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 282 | 272 | 271 |
| Adults (65 years and older) | 230 | 222 | 220 |
| Gender categorical Units: Subjects | | | |
| Female | 245 | 260 | 259 |
| Male | 267 | 234 | 232 |
| Geographical Region Units: Subjects | | | |
| Europe | 473 | 458 | 455 |
| USA | 39 | 36 | 36 |
| ECOG Units: Subjects | | | |
| ECOG=0 | 212 | 196 | 195 |
| ECOG=1 | 300 | 298 | 296 |
| Time from initial diagnosis of advanced disease to randomization (months) Units: Subjects | | | |
| <6 months | 153 | 152 | 151 |
| >=6 months | 359 | 342 | 340 |
| Chemotherapy regimen in study Units: Subjects | | | |
| Gemcitabine and Abraxane | 296 | 283 | 280 |
| Irinotecan and 5-FU/LV | 216 | 211 | 211 |

| Reporting group values | Final Analysis - PRO | Final Analysis - PK | |
|------------------------|----------------------|---------------------|--|
| Number of subjects | 457 | 226 | |

| | | | |
|---|-----|-----|--|
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 249 | 127 | |
| Adults (65 years and older) | 209 | 99 | |
| Gender categorical Units: Subjects | | | |
| Female | 242 | 117 | |
| Male | 215 | 109 | |
| Geographical Region Units: Subjects | | | |
| Europe | 427 | 207 | |
| USA | 30 | 19 | |
| ECOG Units: Subjects | | | |
| ECOG=0 | 184 | 95 | |
| ECOG=1 | 273 | 131 | |
| Time from initial diagnosis of advanced disease to randomization (months) Units: Subjects | | | |
| <6 months | 140 | 74 | |
| >=6 months | 317 | 152 | |
| Chemotherapy regimen in study Units: Subjects | | | |
| Gemcitabine and Abraxane | 270 | 135 | |
| Irinotecan and 5-FU/LV | 187 | 91 | |

End points

End points reporting groups

| | |
|--|-------------------------------|
| Reporting group title | Eryaspase + chemotherapy |
| Reporting group description: Patients randomized to Arm A receive eryaspase in combination with gemcitabine and Abraxane or irinotecan and 5-FU/LV. | |
| Reporting group title | Chemotherapy alone |
| Reporting group description: Patients randomized to Arm B receive either gemcitabine and Abraxane or irinotecan and 5-FU/LV. | |
| Subject analysis set title | Final Analysis |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: The ITT population comprised all patients who were randomized to study treatment, regardless of whether they received study medication. | |
| Subject analysis set title | Final Analysis - Safety |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: The safety population is defined as all patients who received at least one dose of study drug. | |
| Subject analysis set title | Final Analysis - Per Protocol |
| Subject analysis set type | Per protocol |
| Subject analysis set description: The per protocol population is defined as a subset of ITT patients who receive at least one dose of study medication and had no major protocol deviation in inclusion/exclusion criteria. | |
| Subject analysis set title | Final Analysis - PRO |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: The PRO population will consist of all patients who receive at least one dose of the study treatment and provide answers to at least some items of the EORTC QLQ-C30 at Cycle 1 Day 1 (i.e, baseline) and a time point after the date of first dose of study treatment. | |
| Subject analysis set title | Final Analysis - PK |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: The pharmacokinetic analysis set will include all randomized patients who received at least one dose of eryaspase and who have at least one post-baseline PK assessment. | |

Primary: Overall Survival

| | |
|---|------------------|
| End point title | Overall Survival |
| End point description: OS defined as the time elapsed between randomization and death from any cause. Patients who are not known to have died prior to data cut-off will be censored at the date of last contact or clinical cut-off, whichever comes first. | |
| End point type | Primary |
| End point timeframe: 36 months | |

| End point values | Eryaspase + chemotherapy | Chemotherapy alone | | |
|----------------------------------|--------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 255 ^[1] | 257 ^[2] | | |
| Units: months | | | | |
| median (confidence interval 95%) | 7.5 (6.5 to 8.3) | 6.7 (5.4 to 7.5) | | |

Notes:

[1] - ITT population

[2] - ITT population

Statistical analyses

| Statistical analysis title | OS ITT population |
|----------------------------|-------------------|
|----------------------------|-------------------|

Statistical analysis description:

OS is measured from the date of randomization to the date of death from any cause. Patients who are not known to have died are censored at the date of last contact or date of clinical cut-off, whichever comes first. The stratification factors include ECOG performance status (0 or 1), Chemotherapy regimen (gemcitabine/Abraxane or irinotecan-based treatment [FOLFIRI or its equivalent Onivyde/5-FU/LV]), and Time interval since initial diagnosis of advanced disease (<6 months or ≥6 months).

| | |
|---|---|
| Comparison groups | Eryaspase + chemotherapy v Chemotherapy alone |
| Number of subjects included in analysis | 512 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.46 ^[3] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.76 |
| upper limit | 1.11 |

Notes:

[3] - The two-sided p-value for the time to event analysis is associated with the stratified log-rank statistic. The null hypothesis is rejected if the two-sided p-value for the test ≤0.046.

Secondary: Progression Free Survival

| | |
|-----------------|---------------------------|
| End point title | Progression Free Survival |
|-----------------|---------------------------|

End point description:

PFS is defined as the interval time from the date of randomization until objective disease progression per modified RECIST 1.1, or death from any cause in the absence of disease progression, whichever occurs first.

PFS is compared between the two treatment arms using the same methods of analysis as for OS.

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

End point timeframe:

36 months

| End point values | Eryaspase + chemotherapy | Chemotherapy alone | | |
|----------------------------------|--------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 255 | 257 | | |
| Units: month | | | | |
| median (confidence interval 95%) | 3.7 (3.4 to 4.1) | 3.4 (2.0 to 3.7) | | |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | PFS ITT population |
| Statistical analysis description: | |
| Stratified log-rank test, with the stratification variable being ECOG performance status (0 or 1), Chemotherapy regimen (gemcitabine/Abraxane or irinotecan-based treatment [FOLFIRI or its equivalent Onivyde/5-FU/LV]) and Time interval since initial diagnosis of advanced disease (<6 months or ≥6 months). | |
| Comparison groups | Chemotherapy alone v Eryaspase + chemotherapy |
| Number of subjects included in analysis | 512 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.17 ^[4] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.88 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.73 |
| upper limit | 1.07 |

Notes:

[4] - The two-sided p-value for the time to event analysis is associated with the stratified log-rank statistic. The null hypothesis is rejected if the two-sided p-value for this test and proceeding OS test are ≤0.046.

Secondary: Overall Response Rate

| | |
|---|-----------------------|
| End point title | Overall Response Rate |
| End point description: | |
| ORR is defined as the proportion of patients who achieve objective tumor response (CR or PR) per modified RECIST 1.1. | |
| End point type | Secondary |
| End point timeframe: | |
| 36 months | |

| End point values | Eryaspase + chemotherapy | Chemotherapy alone | | |
|-----------------------------|--------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 255 | 257 | | |
| Units: subjects | 41 | 32 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | ORR ITT Population |
| Statistical analysis description: ORR is defined as the proportion of patients who achieve objective tumor response (CR or PR) per modified RECIST 1.1. The 95% CI is calculated using the binomial exact (Clopper-Pearson) method and 2-sided p-value is from the stratified Cochran-Mantel-Haenszel test. The stratification factors are ECOG, chemotherapy regimen, and time interval since initial diagnosis of advanced disease. The null hypothesis is rejected if the 2-sided p-value for this test and proceeding OS and PFS are ≤ 0.046 . | |
| Comparison groups | Eryaspase + chemotherapy v Chemotherapy alone |
| Number of subjects included in analysis | 512 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.242 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.35 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.81 |
| upper limit | 2.24 |

Secondary: Disease Control Rate

| | |
|--|----------------------|
| End point title | Disease Control Rate |
| End point description: DCR is defined as the proportion of patients who achieve CR, PR or SD per modified RECIST 1.1. The denominator for DCR is the number of ITT patients in the treatment group. | |
| End point type | Secondary |
| End point timeframe: 36 months | |

| End point values | Eryaspase + chemotherapy | Chemotherapy alone | | |
|-----------------------------|--------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 255 | 257 | | |
| Units: subjects | 147 | 126 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | DCR ITT Population |
| Comparison groups | Chemotherapy alone v Eryaspase + chemotherapy |
| Number of subjects included in analysis | 512 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[5] |
| P-value | = 0.047 |
| Method | Cochran-Mantel-Haenszel |

Notes:

[5] - The DCR for each treatment group, along with 95% CIs will be calculated. The DCRs will be compared using a stratified CMH test with the same strata as for the primary analysis for OS.

Secondary: Duration of Response ITT population with ORR

| | |
|-----------------|--|
| End point title | Duration of Response ITT population with ORR |
|-----------------|--|

End point description:

DoR is measured from the first reporting of CR or PR per modified RECIST 1.1 until the first date of progression, death, or censoring; Patients who were not known to have disease progression or died were censored to the date of last assessment.

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

End point timeframe:

36 months

| End point values | Eryaspase + chemotherapy | Chemotherapy alone | | |
|----------------------------------|--------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 41 | 32 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 5.7 (3.9 to 7.4) | 5.8 (2.8 to 7.4) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Global Health Status time to event worsening analysis - PRO population

| | |
|-----------------|--|
| End point title | Global Health Status time to event worsening analysis - PRO population |
|-----------------|--|

End point description:

The time to first Worsening is the date of randomization to the date of first Worsening occurred. Patients who did not have any Worsening were censored at date of last measurement or at baseline if no measurement was available post-baseline.

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

End point timeframe:

36 months

| End point values | Eryaspase + chemotherapy | Chemotherapy alone | | |
|----------------------------------|--------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 228 | 229 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 4.0 (3.1 to 5.1) | 3.6 (2.8 to 4.7) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Global Health Status time to event improvement analysis - PRO population

| | |
|-----------------|--|
| End point title | Global Health Status time to event improvement analysis - PRO population |
|-----------------|--|

End point description:

The time to first improvement is the date of randomization to the date of first improvement occurred. Patients who did not have any improvement were censored at date of last measurement or at baseline if no measurement was available post-baseline.

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

End point timeframe:

36 months

| End point values | Eryaspase + chemotherapy | Chemotherapy alone | | |
|----------------------------------|--------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 228 | 229 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 10.6 (3.8 to 12.1) | 5.6 (3.8 to 6.4) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Collected from time of informed consent until 90 days after last study treatment

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 24.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------------------|
| Reporting group title | Eryaspase + chemotherapy |
|-----------------------|--------------------------|

Reporting group description:

Patients randomized to Arm A receive eryaspase in combination with gemcitabine and Abraxane or irinotecan and 5-FU/LV.

| | |
|-----------------------|--------------------|
| Reporting group title | Chemotherapy alone |
|-----------------------|--------------------|

Reporting group description:

Patients randomized to Arm B receive either gemcitabine and Abraxane or irinotecan and 5-FU/LV.

| Serious adverse events | Eryaspase + chemotherapy | Chemotherapy alone | |
|---|--------------------------|--------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 122 / 248 (49.19%) | 105 / 246 (42.68%) | |
| number of deaths (all causes) | 202 | 206 | |
| number of deaths resulting from adverse events | 14 | 9 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer pain | | | |
| subjects affected / exposed | 2 / 248 (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 | |
| Infected neoplasm | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 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 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |

| | | | |
|--|------------------|-----------------|--|
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Superior vena cava syndrome | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vena cava thrombosis | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 10 / 248 (4.03%) | 6 / 246 (2.44%) | |
| occurrences causally related to treatment / all | 3 / 10 | 2 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 7 / 248 (2.82%) | 4 / 246 (1.63%) | |
| occurrences causally related to treatment / all | 4 / 7 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inadequate analgesia | | | |
| subjects affected / exposed | 0 / 248 (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 | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pain | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden death | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Immune system disorders | | | |
| Alloimmunisation | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypersensitivity | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (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 | | | |
| Ovarian cyst ruptured | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostatitis | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 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, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 10 / 248 (4.03%) | 5 / 246 (2.03%) | |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 2 / 248 (0.81%) | 3 / 246 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung disorder | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | 3 / 246 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypersensitivity pneumonitis | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary oedema | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 248 (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 | |
| Pulmonary thrombosis | | | |
| subjects affected / exposed | 0 / 248 (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 failure | | | |
| subjects affected / exposed | 0 / 248 (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 | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 248 (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 | |
| Product issues | | | |
| Device malfunction | | | |
| subjects affected / exposed | 3 / 248 (1.21%) | 4 / 246 (1.63%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Pancreatic enzymes abnormal | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Femur fracture | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemolytic transfusion reaction | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Overdose | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infusion related reaction | | | |
| subjects affected / exposed | 0 / 248 (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 | |
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 248 (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 | |
| Transfusion reaction | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wrist fracture | | | |
| subjects affected / exposed | 0 / 248 (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 | | | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 248 (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 | |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 248 (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 | |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 5 / 246 (2.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 4 / 248 (1.61%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral infarction | | | |
| subjects affected / exposed | 0 / 248 (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 | |
| Encephalopathy | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Facial paresis | | | |
| subjects affected / exposed | 0 / 248 (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 | |
| Neuropathy peripheral | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 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 | 2 / 248 (0.81%) | 4 / 246 (1.63%) | |
| occurrences causally related to treatment / all | 2 / 2 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 3 / 248 (1.21%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 3 / 3 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 3 / 246 (1.22%) | |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |
| subjects affected / exposed | 3 / 248 (1.21%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 2 / 3 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | 3 / 246 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombotic microangiopathy | | | |
| subjects affected / exposed | 2 / 248 (0.81%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemolytic uraemic syndrome | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 2 / 248 (0.81%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Autoimmune haemolytic anaemia | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bicytopenia | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile bone marrow aplasia | | | |
| subjects affected / exposed | 0 / 248 (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 | |
| Myelosuppression | | | |
| subjects affected / exposed | 0 / 248 (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 disorders | | | |
| Gastrointestinal obstruction | | | |
| subjects affected / exposed | 9 / 248 (3.63%) | 11 / 246 (4.47%) | |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 11 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 7 / 248 (2.82%) | 9 / 246 (3.66%) | |
| occurrences causally related to treatment / all | 2 / 7 | 1 / 9 | |
| deaths causally related to treatment / all | 1 / 2 | 0 / 4 | |
| Diarrhoea | | | |
| subjects affected / exposed | 6 / 248 (2.42%) | 5 / 246 (2.03%) | |
| occurrences causally related to treatment / all | 5 / 6 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 6 / 248 (2.42%) | 4 / 246 (1.63%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 3 / 248 (1.21%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 2 / 3 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 2 / 248 (0.81%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 1 / 2 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal ulcer | | | |
| subjects affected / exposed | 2 / 248 (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 | |
| Enteritis | | | |
| subjects affected / exposed | 0 / 248 (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 | |
| Haematemesis | | | |
| subjects affected / exposed | 0 / 248 (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 | 1 / 248 (0.40%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic colitis | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oral disorder | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 248 (0.81%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal stenosis | | | |
| subjects affected / exposed | 0 / 248 (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 | |
| Gastric varices | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 248 (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 | |
| Melaena | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal haemorrhage | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatic duct stenosis | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pancreatitis relapsing | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 0 / 248 (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 | |
| Intestinal ischaemia | | | |
| subjects affected / exposed | 0 / 248 (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 | |
| Large intestine perforation | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholangitis | | | |
| subjects affected / exposed | 13 / 248 (5.24%) | 5 / 246 (2.03%) | |
| occurrences causally related to treatment / all | 0 / 13 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bile duct stenosis | | | |
| subjects affected / exposed | 2 / 248 (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 | |
| Cholestasis | | | |
| subjects affected / exposed | 2 / 248 (0.81%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 2 / 248 (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 | |
| Jaundice cholestatic | | | |
| subjects affected / exposed | 0 / 248 (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 | |
| Acute hepatic failure | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 248 (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 | |
| Biliary dilatation | | | |
| subjects affected / exposed | 0 / 248 (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 | |
| Biliary obstruction | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Biliary tract infection | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholangitis acute | | | |
| subjects affected / exposed | 0 / 248 (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 | 1 / 248 (0.40%) | 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 cytolysis | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 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 failure | | | |
| subjects affected / exposed | 0 / 248 (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 | |
| Portal vein thrombosis | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 1 / 248 (0.40%) | 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 | | | |
| Renal failure | | | |
| subjects affected / exposed | 4 / 248 (1.61%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 248 (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 | |
| Infections and infestations | | | |
| Sepsis | | | |
| subjects affected / exposed | 11 / 248 (4.44%) | 6 / 246 (2.44%) | |
| occurrences causally related to treatment / all | 0 / 11 | 1 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 3 / 248 (1.21%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 4 / 248 (1.61%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Bacteraemia | | | |
| subjects affected / exposed | 2 / 248 (0.81%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Aeromonas infection | | | |
| subjects affected / exposed | 2 / 248 (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 | |
| Atypical pneumonia | | | |
| subjects affected / exposed | 2 / 248 (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 | |
| COVID-19 | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Infection | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver abscess | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal abscess | | | |
| subjects affected / exposed | 0 / 248 (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 abscess | | | |
| subjects affected / exposed | 0 / 248 (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 | |
| COVID-19 pneumonia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic infection | | | |
| subjects affected / exposed | 0 / 248 (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 | |
| Paronychia | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Perihepatic abscess | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral discitis | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 0 / 248 (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 / 1 | |
| Pneumonia haemophilus | | | |
| subjects affected / exposed | 0 / 248 (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 | |
| Subcutaneous abscess | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Superinfection | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (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 | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 2 / 248 (0.81%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Food intolerance | | | |
| subjects affected / exposed | 0 / 248 (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 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malnutrition | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 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 | Eryaspase + chemotherapy | Chemotherapy alone | |
|---|-------------------------------------|---------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 248 / 248 (100.00%) | 242 / 246 (98.37%) | |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 35 / 248 (14.11%) | 14 / 246 (5.69%) | |
| occurrences (all) | 35 | 14 | |
| Transaminases increased | | | |
| subjects affected / exposed | 30 / 248 (12.10%) | 18 / 246 (7.32%) | |
| occurrences (all) | 30 | 18 | |
| Blood albumin decreased | | | |
| subjects affected / exposed | 15 / 248 (6.05%) | 16 / 246 (6.50%) | |
| occurrences (all) | 15 | 16 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 16 / 248 (6.45%) | 13 / 246 (5.28%) | |
| occurrences (all) | 16 | 13 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 15 / 248 (6.05%) | 10 / 246 (4.07%) | |
| occurrences (all) | 15 | 10 | |
| Nervous system disorders | | | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 69 / 248 (27.82%) | 62 / 246 (25.20%) | |
| occurrences (all) | 69 | 62 | |
| Headache | | | |
| subjects affected / exposed | 29 / 248 (11.69%) | 14 / 246 (5.69%) | |
| occurrences (all) | 29 | 14 | |
| Dysgeusia | | | |
| subjects affected / exposed | 20 / 248 (8.06%) | 14 / 246 (5.69%) | |
| occurrences (all) | 20 | 14 | |
| Dizziness | | | |
| subjects affected / exposed | 12 / 248 (4.84%) | 10 / 246 (4.07%) | |
| occurrences (all) | 12 | 10 | |
| General disorders and administration site conditions | | | |

| | | | |
|--------------------------------------|--------------------|--------------------|--|
| Asthenia | | | |
| subjects affected / exposed | 186 / 248 (75.00%) | 173 / 246 (70.33%) | |
| occurrences (all) | 186 | 173 | |
| Pyrexia | | | |
| subjects affected / exposed | 73 / 248 (29.44%) | 56 / 246 (22.76%) | |
| occurrences (all) | 73 | 56 | |
| Oedema | | | |
| subjects affected / exposed | 65 / 248 (26.21%) | 47 / 246 (19.11%) | |
| occurrences (all) | 65 | 47 | |
| Chills | | | |
| subjects affected / exposed | 17 / 248 (6.85%) | 6 / 246 (2.44%) | |
| occurrences (all) | 17 | 6 | |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 108 / 248 (43.55%) | 93 / 246 (37.80%) | |
| occurrences (all) | 108 | 93 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 75 / 248 (30.24%) | 72 / 246 (29.27%) | |
| occurrences (all) | 75 | 72 | |
| Leukopenia | | | |
| subjects affected / exposed | 28 / 248 (11.29%) | 16 / 246 (6.50%) | |
| occurrences (all) | 28 | 16 | |
| Lymphopenia | | | |
| subjects affected / exposed | 19 / 248 (7.66%) | 10 / 246 (4.07%) | |
| occurrences (all) | 19 | 10 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 133 / 248 (53.63%) | 107 / 246 (43.50%) | |
| occurrences (all) | 133 | 107 | |
| Nausea | | | |
| subjects affected / exposed | 132 / 248 (53.23%) | 89 / 246 (36.18%) | |
| occurrences (all) | 132 | 89 | |
| Abdominal pain | | | |
| subjects affected / exposed | 96 / 248 (38.71%) | 84 / 246 (34.15%) | |
| occurrences (all) | 96 | 84 | |
| Constipation | | | |

| | | | |
|---|-------------------|-------------------|--|
| subjects affected / exposed | 69 / 248 (27.82%) | 62 / 246 (25.20%) | |
| occurrences (all) | 69 | 62 | |
| Vomiting | | | |
| subjects affected / exposed | 69 / 248 (27.82%) | 57 / 246 (23.17%) | |
| occurrences (all) | 69 | 57 | |
| Oral disorder | | | |
| subjects affected / exposed | 58 / 248 (23.39%) | 60 / 246 (24.39%) | |
| occurrences (all) | 58 | 60 | |
| Flatulence | | | |
| subjects affected / exposed | 19 / 248 (7.66%) | 8 / 246 (3.25%) | |
| occurrences (all) | 19 | 8 | |
| Ascites | | | |
| subjects affected / exposed | 15 / 248 (6.05%) | 7 / 246 (2.85%) | |
| occurrences (all) | 15 | 7 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 15 / 248 (6.05%) | 5 / 246 (2.03%) | |
| occurrences (all) | 15 | 5 | |
| Dyspepsia | | | |
| subjects affected / exposed | 12 / 248 (4.84%) | 7 / 246 (2.85%) | |
| occurrences (all) | 12 | 7 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 34 / 248 (13.71%) | 24 / 246 (9.76%) | |
| occurrences (all) | 34 | 24 | |
| Epistaxis | | | |
| subjects affected / exposed | 21 / 248 (8.47%) | 16 / 246 (6.50%) | |
| occurrences (all) | 21 | 16 | |
| Cough | | | |
| subjects affected / exposed | 14 / 248 (5.65%) | 11 / 246 (4.47%) | |
| occurrences (all) | 14 | 11 | |
| Hepatobiliary disorders | | | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 18 / 248 (7.26%) | 10 / 246 (4.07%) | |
| occurrences (all) | 18 | 10 | |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|--|-------------------|-------------------|--|
| Alopecia subjects affected / exposed occurrences (all) | 64 / 248 (25.81%) | 51 / 246 (20.73%) | |
| | 64 | 51 | |
| | | | |
| | | | |
| Rash subjects affected / exposed occurrences (all) | 18 / 248 (7.26%) | 10 / 246 (4.07%) | |
| | 18 | 10 | |
| | | | |
| | | | |
| Pruritus subjects affected / exposed occurrences (all) | 11 / 248 (4.44%) | 13 / 246 (5.28%) | |
| | 11 | 13 | |
| | | | |
| | | | |
| Dry skin subjects affected / exposed occurrences (all) | 15 / 248 (6.05%) | 7 / 246 (2.85%) | |
| | 15 | 7 | |
| | | | |
| | | | |
| | | | |
| Psychiatric disorders Sleep disorder subjects affected / exposed occurrences (all) | 16 / 248 (6.45%) | 19 / 246 (7.72%) | |
| | 16 | 19 | |
| | | | |
| | | | |
| Anxiety subjects affected / exposed occurrences (all) | 13 / 248 (5.24%) | 13 / 246 (5.28%) | |
| | 13 | 13 | |
| | | | |
| | | | |
| | | | |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 37 / 248 (14.92%) | 24 / 246 (9.76%) | |
| | 37 | 24 | |
| | | | |
| | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 22 / 248 (8.87%) | 21 / 246 (8.54%) | |
| | 22 | 21 | |
| | | | |
| | | | |
| Myalgia subjects affected / exposed occurrences (all) | 25 / 248 (10.08%) | 16 / 246 (6.50%) | |
| | 25 | 16 | |
| | | | |
| | | | |
| Pain in extremity subjects affected / exposed occurrences (all) | 12 / 248 (4.84%) | 10 / 246 (4.07%) | |
| | 12 | 10 | |
| | | | |
| | | | |
| | | | |
| Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all) | 12 / 248 (4.84%) | 13 / 246 (5.28%) | |
| | 12 | 13 | |
| | | | |
| | | | |

| | | | |
|---|-------------------------|-------------------------|--|
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 12 / 248 (4.84%) 12 | 10 / 246 (4.07%) 10 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 76 / 248 (30.65%) 76 | 60 / 246 (24.39%) 60 | |
| Hypokalaemia subjects affected / exposed occurrences (all) | 29 / 248 (11.69%) 29 | 26 / 246 (10.57%) 26 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 05 September 2019 | Key changes included: Clearly defined objectives and study endpoints. Extension of safety assessments from 30 days to 90 days or start of new anti-cancer treatment. Detail acceptable birth control methods. Aligned pre-testing and dosing guidance for UGT1A1 and DPD deficiency as per product labels for irinotecan and 5-FU. Clarified Onivyde dosing. Update of specific toxicity management. Other clarifications and administrative changes per sites questions. |
| 06 February 2021 | Key changes included: Reduced frequency of ECG assessment during study. COVID-19 impact to waive certain assessments, use of facilities not defined in the clinical information forms, documentation of protocol deviations resulting from COVID-19 impact, and allowing of remote monitoring visits in case of site visit and travel restrictions. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported