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 committed 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	64 / 248 (25.81%)	51 / 246 (20.73%)	
occurrences (all)	64	51	
Rash			
subjects affected / exposed	18 / 248 (7.26%)	10 / 246 (4.07%)	
occurrences (all)	18	10	
Pruritus			
subjects affected / exposed	11 / 248 (4.44%)	13 / 246 (5.28%)	
occurrences (all)	11	13	
Dry skin			
subjects affected / exposed	15 / 248 (6.05%)	7 / 246 (2.85%)	
occurrences (all)	15	7	
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	16 / 248 (6.45%)	19 / 246 (7.72%)	
occurrences (all)	16	19	
Anxiety			
subjects affected / exposed	13 / 248 (5.24%)	13 / 246 (5.28%)	
occurrences (all)	13	13	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	37 / 248 (14.92%)	24 / 246 (9.76%)	
occurrences (all)	37	24	
Arthralgia			
subjects affected / exposed	22 / 248 (8.87%)	21 / 246 (8.54%)	
occurrences (all)	22	21	
Myalgia			
subjects affected / exposed	25 / 248 (10.08%)	16 / 246 (6.50%)	
occurrences (all)	25	16	
Pain in extremity			
subjects affected / exposed	12 / 248 (4.84%)	10 / 246 (4.07%)	
occurrences (all)	12	10	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	12 / 248 (4.84%)	13 / 246 (5.28%)	
occurrences (all)	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) Hypokalaemia subjects affected / exposed occurrences (all)	 76 / 248 (30.65%) 76 29 / 248 (11.69%) 29	 60 / 246 (24.39%) 60 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