Clinical trial results:
Phase II randomized study evaluation of FOLFIRINOX +/- LV5FU2 in maintenance and FIRGEM in 1rst line of metastatic pancreas cancer

Summary

EudraCT number	2014-002574-36
Trial protocol	FR
Global end of trial date	10 August 2021

Results information

Result version number	v1 (current)
This version publication date	05 October 2024
First version publication date	05 October 2024

Trial information

Trial identification

Sponsor protocol code	PRODIGE35

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Fédération Francophone de Cancérologie Digestive (FFCD)
Sponsor organisation address	7 Bd Jeanne d'Arc, Dijon, France, 21000
Public contact	Head of Biostatistics, Fédération Francophone de Cancérologie Digestive, +33 380393479, karine.le-malicot@u-bourgogne.fr
Scientific contact	Head of Biostatistics, Fédération Francophone de Cancérologie Digestive, +33 380393479, karine.le-malicot@u-bourgogne.fr

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	08 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 December 2017
Global end of trial reached?	Yes
Global end of trial date	10 August 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

In this randomized phase II study, patients with metastatic pancreatic cancer were randomly assigned to receive either 6 months of FOLFIRINOX (arm A), 4 months of FOLFIRINOX followed by leucovorin plus fluorouracil maintenance treatment for controlled patients (arm B), or a sequential treatment alternating gemcitabine and fluorouracil, leucovorin, and irinotecan every 2 months (arm C). The primary end point was progression-free survival at 6 months.

Main objective is to evaluate, in each arm, the patient rate in live and without radiological and or clinical progression at 6 months after randomization,

Protection of trial subjects:

The study was done in accordance with the Declaration of Helsinki (amended 2000) and the International Conference on Harmonization of Technical Requirements of Pharmaceuticals for Human Use (ICH) Note for Guidance on Good Clinical Practice and approved by the appropriate Ethics Committees.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 December 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 273
Worldwide total number of subjects	273
EEA total number of subjects	273

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)	138
From 65 to 84 years	135
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between January 2015 and November 2016, 276 patients were randomly assigned to either Folfirinox (Arm A), Folfirinox (8 cures) then LV5FU2 (maintenance) then Folfirinox if progression (Arm B) or FIRGEM (alternating 2 months of FOLFIRI and 2 months of GEMCITABINE) (Arm C)

Pre-assignment

Screening details:

Patients were eligible to be included in this study if they had histologically confirmed mPC and measurable metastases; had received no previous chemotherapy or radiotherapy; and had an ECOG performance status of 0 or 1, an adequate bone marrow reserve, and adequate liver and renal function.

Pre-assignment period milestones

Number of subjects started	273
Number of subjects completed	273

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A - FOLFIRINOX

Arm description:

FOLFIRINOX, cures administered every 2 weeks up to a maximum of 12 cures.

Arm type	Active comparator
Investigational medicinal product name	FOLFIRINOX
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

- Oxaliplatin 85 mg/m2 D1 over 2h, then
- Irinotecan 180 mg/m2 D1 over 90 min
- Folinic acid 400 mg/m2, D1 in 2h (during irinotecan infusion)
- 5-FU bolus 400 mg/m² D1 followed by continuous 5-FU 2400 mg/m2 in total over 46 hours, i.e. 1200 mg/m2 on D1 and 1200 mg/m² on D2.

Arm title	ARM B - FOLFIRINOX with simplified LV5FU2 maintenance

Arm description:

FOLFIRINOX with simplified LV5FU2 maintenance (Arm B)

Arm type	Experimental
Investigational medicinal product name	FOLFIRINOX + LV5FU2
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

FOLFIRINOX for 4 months (8 courses, 1 course every 2 weeks), then if disease is controlled (stable or

objective response (CR or PR)), simplified LV5FU2 (1 course every 2 weeks) in maintenance until progression.

FOLFIRINOX at the same doses as described above for arm A.

LV5FU2 simplified maintenance until progression:
- Folinic acid 400 mg/m² (200 mg/m² if Elvorine), 2-hour infusion followed by
- 5FU 400 mg/m² bolus over 10 min, followed by 5FU 2400 mg/m² infusion over 46 hours.

Arm title	Arm C - FIRGEM

Arm description:

Alternate every 2 months with FOLFIRI.3 (4 courses, 1 course every 2 weeks) and gemcitabine 1000 mg/m2 (2 cycles of 3 courses, one course per week 3 weeks out of 4).

Arm type	Experimental
Investigational medicinal product name	FIRGEM
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

FOLFIRI.3 :
- Irinotecan 90 mg/m² on D1 as a 60-minute infusion in Y of folinic acid,
- Folinic acid 400 mg/m² (or 200 mg/m² Elvorine) on D1 as a 2-hour infusion
- Continuous 5FU 2000 mg/m² for 46 hours
- Then irinotecan 90 mg/m² (1h) on D3, at the end of the 5-FU infusion.

GEMCITABINE:
- 1000 mg/m² infused over 30 min on D1, D8, D15, D29, D36 and D43 for 2 months (1 injection per week for 3 weeks, followed by 7 days' rest (1 week) and resumption of 1 injection per week for 3 weeks).

In the event of progression or limiting toxicity with one of the two treatments, it is recommended (unless contraindicated or refused) to continue with the other treatment until progression, unacceptable toxicity or patient refusal.

Number of subjects in period 1	Arm A - FOLFIRINOX	ARM B - FOLFIRINOX with simplified LV5FU2 maintenance	Arm C - FIRGEM
Started	91	92	90
Treated Patient	87	91	88
Completed	87	91	88
Not completed	4	1	2
Adverse event, serious fatal	1	1	-
Adverse event, non-fatal	3	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Arm A - FOLFIRINOX
Reporting group description:	
FOLFIRINOX, cures administered every 2 weeks up to a maximum of 12 cures.	
Reporting group title	ARM B - FOLFIRINOX with simplified LV5FU2 maintenance
Reporting group description:	
FOLFIRINOX with simplified LV5FU2 maintenance (Arm B)	
Reporting group title	Arm C - FIRGEM
Reporting group description:	
Alternate every 2 months with FOLFIRI.3 (4 courses, 1 course every 2 weeks) and gemcitabine 1000 mg/m2 (2 cycles of 3 courses, one course per week 3 weeks out of 4).	

Reporting group values	Arm A - FOLFIRINOX	ARM B - FOLFIRINOX with simplified LV5FU2 maintenance	Arm C - FIRGEM
Number of subjects	91	92	90
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	46	51	41
From 65-84 years	45	41	49
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	62.57	63.52	64.07
full range (min-max)	39.9 to 75.97	40.32 to 75.27	45.21 to 75.64
Gender categorical Units: Subjects			
Female	35	34	43
Male	56	58	47

Reporting group values	Total		
Number of subjects	273		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	138		
From 65-84 years	135		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
full range (min-max)	-		
Gender categorical			
Units: Subjects			
Female	112		
Male	161		

Subject analysis sets

Subject analysis set title	mITT for efficacy (Arm B)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

mITT for efficacy (Arm B) is defined as patients randomized in arm B whatever the inclusion and noninclusion criteria and who took at least one dose of treatment.

Subject analysis set title	mITT for efficacy (Arm C)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

mITT for efficacy (Arm C) is defined as patients randomized in arm C whatever the inclusion and noninclusion criteria and who took at least one dose of treatment.

Reporting group values	mITT for efficacy (Arm B)	mITT for efficacy (Arm C)	
Number of subjects	91	88	
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	50	40	
From 65-84 years	41	48	
85 years and over			
Age continuous			
Units: years			
arithmetic mean			
full range (min-max)			
Gender categorical			
Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	Arm A - FOLFIRINOX
Reporting group description:	
FOLFIRINOX, cures administered every 2 weeks up to a maximum of 12 cures.	
Reporting group title	ARM B - FOLFIRINOX with simplified LV5FU2 maintenance
Reporting group description:	
FOLFIRINOX with simplified LV5FU2 maintenance (Arm B)	
Reporting group title	Arm C - FIRGEM
Reporting group description:	
Alternate every 2 months with FOLFIRI.3 (4 courses, 1 course every 2 weeks) and gemcitabine 1000 mg/m2 (2 cycles of 3 courses, one course per week 3 weeks out of 4).	
Subject analysis set title	mITT for efficacy (Arm B)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
mITT for efficacy (Arm B) is defined as patients randomized in arm B whatever the inclusion and noninclusion criteria and who took at least one dose of treatment.	
Subject analysis set title	mITT for efficacy (Arm C)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
mITT for efficacy (Arm C) is defined as patients randomized in arm C whatever the inclusion and noninclusion criteria and who took at least one dose of treatment.	

Primary: rate of patients alive without progression at 6 months

End point title	rate of patients alive without progression at 6 months[1]
End point description:	
The primary end point was 6-month PFS rate in each arm and served to determine the better treatment for further trials. In the 91 ittm patients in arm B: If 35 or more patients are alive without progression at 6 months, we conclude that the treatment is effective. In the 88 ittm patients in arm C: If 34 or more patients are alive without progression at 6 months, we conclude that the treatment is effective.	
End point type	Primary
End point timeframe:	
At 6 months	
Notes:	
[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: This is a non-comparative study, so there are no inferential statistics.	

End point values	mITT for efficacy (Arm B)	mITT for efficacy (Arm C)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	91	88		
Units: Patients				
number (not applicable)				
Alive without progression	39	30		
Progression and/or death	52	58		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

End point type	Secondary

End point timeframe:

Until the end of the follow-up or death (Whatever the cause)

End point values	Arm A - FOLFIRINOX	ARM B - FOLFIRINOX with simplified LV5FU2 maintenance	Arm C - FIRGEM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	91	92	90	
Units: Months				
median (confidence interval 95%)	10.1 (8.5 to 12.2)	11.2 (9.0 to 13.1)	7.3 (5.7 to 9.5)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs (related and unrelated, expected and unexpected) occurring in the course of the study, from the signature of the informed consent form and until 30 days after the last dose of the study drug were reported by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	NCI CTC
Dictionary version	4.0

Reporting groups

Reporting group title	Safety Population

Reporting group description:

The safety population is defined as all patients included in the study, regardless of eligibility criteria, who actually received at least one dose of the treatment allocated to them.

Serious adverse events	Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	141 / 266 (53.01%)		
number of deaths (all causes)	245		
number of deaths resulting from adverse events	2		
Vascular disorders			
Thromboembolic event			
subjects affected / exposed	14 / 266 (5.26%)		
occurrences causally related to treatment / all	14 / 14		
deaths causally related to treatment / all	0 / 0		
Hematoma			
subjects affected / exposed	1 / 266 (0.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	1 / 266 (0.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypotension			

subjects affected / exposed	1 / 266 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Superior vena cava syndrome				
subjects affected / exposed	1 / 266 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Pain				
subjects affected / exposed	1 / 266 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Non-cardiac chest pain				
subjects affected / exposed	1 / 266 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	39 / 266 (14.66%)			
occurrences causally related to treatment / all	39 / 39			
deaths causally related to treatment / all	0 / 0			
fever				
subjects affected / exposed	10 / 266 (3.76%)			
occurrences causally related to treatment / all	10 / 10			
deaths causally related to treatment / all	0 / 0			
Chills				
subjects affected / exposed	1 / 266 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Flu symptoms				
subjects affected / exposed	1 / 266 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				

Respiratory, thoracic and mediastinal disorders				
subjects affected / exposed	1 / 266 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	3 / 266 (1.13%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	1 / 266 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Epistaxis				
subjects affected / exposed	1 / 266 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Laryngospasm				
subjects affected / exposed	1 / 266 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	1 / 266 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Mental confusion				
subjects affected / exposed	1 / 266 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Depression				
subjects affected / exposed	3 / 266 (1.13%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			

Investigations			
Bilirubin conjugated increased			
subjects affected / exposed	7 / 266 (2.63%)		
occurrences causally related to treatment / all	7 / 7		
deaths causally related to treatment / all	0 / 0		
Creatinine urine increased			
subjects affected / exposed	2 / 266 (0.75%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
white blood cells decreased			
subjects affected / exposed	1 / 266 (0.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
anemia			
subjects affected / exposed	6 / 266 (2.26%)		
occurrences causally related to treatment / all	6 / 6		
deaths causally related to treatment / all	0 / 0		
Neutrophil count decreased			
subjects affected / exposed	6 / 266 (2.26%)		
occurrences causally related to treatment / all	6 / 6		
deaths causally related to treatment / all	0 / 0		
Weight loss			
subjects affected / exposed	1 / 266 (0.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
platelet decreased			
subjects affected / exposed	3 / 266 (1.13%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	1 / 266 (0.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural			

complications				
Injury, poisoning and procedural complication, other				
subjects affected / exposed	2 / 266 (0.75%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Cardiac arrest				
subjects affected / exposed	1 / 266 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Acute coronary syndrome				
subjects affected / exposed	1 / 266 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Sinus tachycardia				
subjects affected / exposed	1 / 266 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Transient ischaemic attack				
subjects affected / exposed	1 / 266 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Neurotoxicity				
subjects affected / exposed	1 / 266 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cognitive disorder				
subjects affected / exposed	1 / 266 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Hypocellular bone marrow				

subjects affected / exposed	2 / 266 (0.75%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	3 / 266 (1.13%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Gastrointestinal disorder				
subjects affected / exposed	1 / 266 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	3 / 266 (1.13%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	5 / 266 (1.88%)			
occurrences causally related to treatment / all	5 / 5			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	22 / 266 (8.27%)			
occurrences causally related to treatment / all	22 / 22			
deaths causally related to treatment / all	0 / 0			
Stomach ache				
subjects affected / exposed	4 / 266 (1.50%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	24 / 266 (9.02%)			
occurrences causally related to treatment / all	24 / 24			
deaths causally related to treatment / all	0 / 0			
Lower gastrointestinal haemorrhage				

subjects affected / exposed	3 / 266 (1.13%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Upper gastrointestinal haemorrhage			
subjects affected / exposed	3 / 266 (1.13%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Rectal haemorrhage			
subjects affected / exposed	2 / 266 (0.75%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Inflammation of the mucosa of the small intestine			
subjects affected / exposed	1 / 266 (0.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Oral mucosa			
subjects affected / exposed	3 / 266 (1.13%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	10 / 266 (3.76%)		
occurrences causally related to treatment / all	10 / 10		
deaths causally related to treatment / all	0 / 0		
Obstruction of the small intestine			
subjects affected / exposed	1 / 266 (0.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Colon obstruction			
subjects affected / exposed	13 / 266 (4.89%)		
occurrences causally related to treatment / all	13 / 13		
deaths causally related to treatment / all	0 / 0		
Duodenal occlusion			

subjects affected / exposed	5 / 266 (1.88%)			
occurrences causally related to treatment / all	5 / 5			
deaths causally related to treatment / all	0 / 0			
Oesophagitis				
subjects affected / exposed	2 / 266 (0.75%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	2 / 266 (0.75%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Small intestinal perforation				
subjects affected / exposed	2 / 266 (0.75%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Gastric perforation				
subjects affected / exposed	1 / 266 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Duodenal stenosis				
subjects affected / exposed	2 / 266 (0.75%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	26 / 266 (9.77%)			
occurrences causally related to treatment / all	26 / 26			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
hepatobiliary disorder				
subjects affected / exposed	11 / 266 (4.14%)			
occurrences causally related to treatment / all	11 / 11			
deaths causally related to treatment / all	0 / 0			
hepatalgia				

subjects affected / exposed	1 / 266 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gallbladder obstruction				
subjects affected / exposed	3 / 266 (1.13%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Palmar-plantar erythrodysaesthesia syndrome				
subjects affected / exposed	1 / 266 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
hematuria				
subjects affected / exposed	1 / 266 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Acute renal lesion				
subjects affected / exposed	2 / 266 (0.75%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Urinary retention				
subjects affected / exposed	1 / 266 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Arthritis				
subjects affected / exposed	1 / 266 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Back pain				

subjects affected / exposed	3 / 266 (1.13%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Bone pain				
subjects affected / exposed	1 / 266 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Urinary tract infection				
subjects affected / exposed	1 / 266 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Catheter-related infection				
subjects affected / exposed	6 / 266 (2.26%)			
occurrences causally related to treatment / all	6 / 6			
deaths causally related to treatment / all	0 / 0			
Peritoneal infection				
subjects affected / exposed	1 / 266 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
pulmonary infection				
subjects affected / exposed	3 / 266 (1.13%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
renal infection				
subjects affected / exposed	1 / 266 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Biliary tract infection				
subjects affected / exposed	5 / 266 (1.88%)			
occurrences causally related to treatment / all	5 / 5			
deaths causally related to treatment / all	0 / 0			
Infections and infestation, other				

subjects affected / exposed	2 / 266 (0.75%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Septicemia				
subjects affected / exposed	15 / 266 (5.64%)			
occurrences causally related to treatment / all	15 / 15			
deaths causally related to treatment / all	1 / 1			
Metabolism and nutrition disorders				
anorexia				
subjects affected / exposed	13 / 266 (4.89%)			
occurrences causally related to treatment / all	13 / 13			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	4 / 266 (1.50%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Hyperglycaemia				
subjects affected / exposed	1 / 266 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypernatraemia				
subjects affected / exposed	1 / 266 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypocalcaemia				
subjects affected / exposed	1 / 266 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypokalaemia				
subjects affected / exposed	3 / 266 (1.13%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				

subjects affected / exposed	1 / 266 (0.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders, other			
subjects affected / exposed	1 / 266 (0.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		

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

Non-serious adverse events	Safety Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	266 / 266 (100.00%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	168 / 266 (63.16%)		
occurrences (all)	168		
Aspartate aminotransferase increased			
subjects affected / exposed	174 / 266 (65.41%)		
occurrences (all)	174		
Bilirubin conjugated increased			
subjects affected / exposed	69 / 266 (25.94%)		
occurrences (all)	69		
Creatine urine increased			
subjects affected / exposed	25 / 266 (9.40%)		
occurrences (all)	25		
Gamma-glutamyltransferase increased			
subjects affected / exposed	142 / 266 (53.38%)		
occurrences (all)	142		
White blood cell count decreased			
subjects affected / exposed	54 / 266 (20.30%)		
occurrences (all)	54		
Anaemia			

subjects affected / exposed	254 / 266 (95.49%)		
occurrences (all)	254		
Neutrophil count decreased			
subjects affected / exposed	152 / 266 (57.14%)		
occurrences (all)	152		
Lymphocyte count decreased			
subjects affected / exposed	62 / 266 (23.31%)		
occurrences (all)	62		
alkaline phosphatase increased			
subjects affected / exposed	222 / 266 (83.46%)		
occurrences (all)	222		
Weight decreased			
subjects affected / exposed	57 / 266 (21.43%)		
occurrences (all)	57		
Platelet count decreased			
subjects affected / exposed	170 / 266 (63.91%)		
occurrences (all)	170		
Vascular disorders			
thromboembolic event			
subjects affected / exposed	22 / 266 (8.27%)		
occurrences (all)	22		
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	15 / 266 (5.64%)		
occurrences (all)	15		
Neurotoxicity			
subjects affected / exposed	146 / 266 (54.89%)		
occurrences (all)	146		
General disorders and administration site conditions			
Fever			
subjects affected / exposed	66 / 266 (24.81%)		
occurrences (all)	66		
Fatigue			
subjects affected / exposed	226 / 266 (84.96%)		
occurrences (all)	226		
Oedema of the limbs			

subjects affected / exposed occurrences (all)	25 / 266 (9.40%) 25		
Immune system disorders allergic reaction subjects affected / exposed occurrences (all)	 14 / 266 (5.26%) 14		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Stomach pain subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Oral Mucositis subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 87 / 266 (32.71%) 87 204 / 266 (76.69%) 204 25 / 266 (9.40%) 25 116 / 266 (43.61%) 116 79 / 266 (29.70%) 79 203 / 266 (76.32%) 203 144 / 266 (54.14%) 144		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	 20 / 266 (7.52%) 20		
Skin and subcutaneous tissue disorders Skin disorder subjects affected / exposed occurrences (all)	 18 / 266 (6.77%) 18		

Alopecia			
subjects affected / exposed	61 / 266 (22.93%)		
occurrences (all)	61		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	26 / 266 (9.77%)		
occurrences (all)	26		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	23 / 266 (8.65%)		
occurrences (all)	23		
Myalgia			
subjects affected / exposed	18 / 266 (6.77%)		
occurrences (all)	18		
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	146 / 266 (54.89%)		
occurrences (all)	146		
Hyperglycaemia			
subjects affected / exposed	36 / 266 (13.53%)		
occurrences (all)	36		
Hyperkalaemia			
subjects affected / exposed	34 / 266 (12.78%)		
occurrences (all)	34		
Hypoalbuminaemia			
subjects affected / exposed	63 / 266 (23.68%)		
occurrences (all)	63		
Hypocalcaemia			
subjects affected / exposed	29 / 266 (10.90%)		
occurrences (all)	29		
Hypokalaemia			
subjects affected / exposed	41 / 266 (15.41%)		
occurrences (all)	41		
Hyponatraemia			
subjects affected / exposed	40 / 266 (15.04%)		
occurrences (all)	40		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported