



## Clinical trial results:

### Phase III Multicenter Randomized Study Comparing the Effect of a 6-month Adjuvant Chemotherapy With Gemcitabine-Oxaliplatin to Observation in Patients Who Underwent Surgery for Biliary Tract Cancers

#### Summary

EudraCT number	2008-004560-39
Trial protocol	FR
Global end of trial date	20 February 2019

#### Results information

Result version number	v1 (current)
This version publication date	03 June 2022
First version publication date	03 June 2022

#### Trial information

##### Trial identification

Sponsor protocol code	ACCORD 18/0803
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01313377
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Unicancer
Sponsor organisation address	101 rue de Tolbiac, Paris, France, 75013
Public contact	Nourredine AIT-RAHMOUNE, Unicancer, 33 1 71 93 67 04, n.ait-rahmoune@unicancer.fr
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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 June 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	20 February 2019
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objectives of the Prodiges 12 – Accord 18 study were:

- To evaluate the effect of Gemcitabine – Oxaliplatin adjuvant chemotherapy (GEMOX) on Relapse-Free Survival (RFS) in resected Biliary Tract Cancer (BTC) patients compare to clinical observation.
- To compare Quality Of Life (QoL) in GEMOX-treated resected BTC patients versus clinical observation.

This trial considered RFS as the primary endpoint (the calculation of the number of subjects required and the design of the study are based on this endpoint) and the quality of life as the secondary primary endpoint (power calculation). This is not a composite criterion integrating recurrence and QoL. There are therefore two independently analyzed endpoints.

Protection of trial subjects:

In order to ensure the protection of the rights, safety and well-being of trial subjects, this clinical trial was conducted in accordance with the Declaration of Helsinki (1964) and subsequent amendments, ICH Good Clinical Practice Guidelines (CPMP/ICH/135/95), the European Directive (2001/20/CE) and the applicable local regulatory requirements and laws.

Furthermore, an independent Ethics Committees reviewed and gave a favorable opinion to the study documents, including the initial protocol and all subsequent amendments, and all information and documents provided to subjects/patients.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 September 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	France: 194
Worldwide total number of subjects	194
EEA total number of subjects	194

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	115
From 65 to 84 years	79
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Prodige 12 – Accord 18 was a randomized phase III, double arm, multicenter trial designed to compare the effect of the adjuvant chemotherapy of Gemcitabine-Oxaliplatin for 6 months versus observation on Relapse Free Survival and Quality of life in treating non-metastatic patients who underwent surgery for Biliary Tract Cancers.

### Pre-assignment

Screening details:

The trial consisted of a screening phase before randomization to establish eligibility, a treatment phase (14-day treatment cycles; 12 cycles), and a long-term follow-up to monitor relapse-free survival, quality of life, disease-free survival, overall survival, and safety.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	GEMOX

Arm description:

The GEMOX regimen consisted by the administration of Gemcitabine Hydrochloride and Oxaliplatin in cycle of two days:

- Gemcitabine Hydrochloride was administered at the dose of 1000mg/m<sup>2</sup> intravenously in 500 mL NaCl 0.9% over 100 minutes (fixed-dose infusion rate, 10 mg/m<sup>2</sup>/min) on Day 1 (D1).
- Oxaliplatin was administered at the dose of 85 mg/m<sup>2</sup> intravenously in 500 mL glucose 5% over 2 hours on D2.

GEMOX was administrated every 14 days for 12 cycles to the patients who met all inclusion criteria, none of the exclusion criteria and were randomized in arm A

Arm type	Experimental
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1000mg/m<sup>2</sup> intravenously in 500 mL NaCl 0.9% over 100 minutes (fixed-dose infusion rate, 10 mg/m<sup>2</sup>/min) on day 1.

Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

85 mg/m<sup>2</sup> intravenously in 500 mL glucose 5% over 2 hours on day 2.

In order to prevent oxaliplatin neurotoxicity, 15-minute infusion with 100 ml of 5% glucose each containing 10 ml of 10% calcium gluconate and 10 ml of 15% magnesium sulfate were required before and after each oxaliplatin infusion.

<b>Arm title</b>	Observation
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

<b>Number of subjects in period 1</b>	GEMOX	Observation
Started	95	99
Completed	32	41
Not completed	63	58
Received <50% of dose during the first 6 cycles	11	-
Did not meet inclusion criteria	11	17
Death	41	41

## Baseline characteristics

### Reporting groups

Reporting group title	GEMOX
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Reporting group description:

The GEMOX regimen consisted by the administration of Gemcitabine Hydrochloride and Oxaliplatin in cycle of two days:

- Gemcitabine Hydrochloride was administered at the dose of 1000mg/m<sup>2</sup> intravenously in 500 mL NaCl 0.9% over 100 minutes (fixed-dose infusion rate, 10 mg/m<sup>2</sup>/min) on Day 1 (D1).

- Oxaliplatin was administered at the dose of 85 mg/m<sup>2</sup> intravenously in 500 mL glucose 5% over 2 hours on D2.

GEMOX was administrated every 14 days for 12 cycles to the patients who met all inclusion criteria, none of the exclusion criteria and were randomized in arm A

Reporting group title	Observation
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Reporting group description: -

Reporting group values	GEMOX	Observation	Total
Number of subjects	95	99	194
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)	55	60	115
From 65-84 years	40	39	79
85 years and over	0	0	0
Age continuous			
Units: years			
median	63	63	
full range (min-max)	33 to 83	40 to 80	-
Gender categorical			
Units: Subjects			
Female	38	49	87
Male	57	50	107
Tumor localization			
Units: Subjects			
Gallbladder	19	23	42
Extrahepatic	30	28	58
Intrahepatic	46	45	91
Unknown	0	3	3

## End points

### End points reporting groups

Reporting group title	GEMOX
Reporting group description: The GEMOX regimen consisted by the administration of Gemcitabine Hydrochloride and Oxaliplatin in cycle of two days: - Gemcitabine Hydrochloride was administered at the dose of 1000mg/m2 intravenously in 500 mL NaCl 0.9% over 100 minutes (fixed-dose infusion rate, 10 mg/m2/min) on Day 1 (D1). - Oxaliplatin was administered at the dose of 85 mg/m2 intravenously in 500 mL glucose 5% over 2 hours on D2. GEMOX was administrated every 14 days for 12 cycles to the patients who met all inclusion criteria, none of the exclusion criteria and were randomized in arm A	
Reporting group title	Observation
Reporting group description: -	

### Primary: Relapse-Free Survival

End point title	Relapse-Free Survival
End point description:	
End point type	Primary
End point timeframe: Relapse-free Survival was evaluated between randomisation to the date of relapse, apparition of a second Biliary tract cancers or death from any cause every 3 months for 2 years then every 6 months for the following 3 years until (up to 5.5 years)	

End point values	GEMOX	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	99		
Units: months				
median (confidence interval 95%)	30.4 (15.4 to 43.0)	18.5 (12.6 to 38.2)		

### Statistical analyses

Statistical analysis title	Relapse-free survival
Comparison groups	GEMOX v Observation
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4724
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.81

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.18

### Primary: Time to global health deterioration

End point title	Time to global health deterioration
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End point description:

End point type	Primary
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End point timeframe:

Time to deterioration was evaluated at Baseline (randomisation), every 3 months for 2 years then every 6 months for the following 3 years.

End point values	GEMOX	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	99		
Units: percent				
number (not applicable)				
Deterioration	26	23		
No deterioration	60	72		
NA	9	4		

### Statistical analyses

Statistical analysis title	Time to deterioration
Comparison groups	GEMOX v Observation
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3899
Method	Logrank

### Secondary: overall survival

End point title	overall survival
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End point description:

End point type	Secondary
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End point timeframe:

From randomization to death (up to 5.5 years)



End point values	GEMOX	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	99		
Units: month				
median (confidence interval 95%)	75.8 (34.4 to 78)	50.8 (38.0 to 78)		

### Statistical analyses

Statistical analysis title	Overall survival
Comparison groups	GEMOX v Observation
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7352
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.86

### Secondary: Disease-free survival

End point title	Disease-free survival
End point description:	
End point type	Secondary
End point timeframe:	
From randomization to disease progression or death (up to 5.5 years)	

End point values	GEMOX	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	99		
Units: month				
median (confidence interval 95%)	30.4 (15.4 to 43.3)	18.5 (12.6 to 38.2)		

## Statistical analyses

<b>Statistical analysis title</b>	Disease-free survival
Comparison groups	GEMOX v Observation
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.466
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.25

## Secondary: Relapse-free survival (prognostic N stage)

End point title	Relapse-free survival (prognostic N stage)
End point description:	
End point type	Secondary
End point timeframe:	
up to 5.5 years	

End point values	GEMOX	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95 <sup>[1]</sup>	99 <sup>[2]</sup>		
Units: month				
median (confidence interval 95%)				
N0	48.8 (17.8 to 78)	47.6 (29.3 to 78)		
N+	16.3 (9.4 to 34.9)	12.4 (6.2 to 16.2)		
NX	45.8 (2.6 to 54.3)	11.2 (2.6 to 48.5)		

Notes:

[1] - N0 (35), N+ (35), NX (11)

[2] - N0 (48), (N+ (36), NX (15)

## Statistical analyses

<b>Statistical analysis title</b>	RFS N0
Comparison groups	GEMOX v Observation
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	1.79

<b>Statistical analysis title</b>	RFS N+
Comparison groups	GEMOX v Observation
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4105
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.35

<b>Statistical analysis title</b>	RFS NX
Comparison groups	GEMOX v Observation
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1387
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	1.33

**Secondary: Relapse-free survival (prognostic resection)**

End point title	Relapse-free survival (prognostic resection)
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End point description:
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End point type	Secondary
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End point timeframe:
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up to 5.5 years
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End point values	GEMOX	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95 <sup>[3]</sup>	99 <sup>[4]</sup>		
Units: month				
median (confidence interval 95%)				
R0	36.2 (21.0 to 48.8)	22.8 (12.6 to 44.3)		
R1	12.3 (8.5 to 17.8)	14.3 (5.1 to 21.6)		

Notes:

[3] - R0 (82), R1 (13)

[4] - R0 (87), R1 (12)

**Statistical analyses**

Statistical analysis title	RFS R0
Comparison groups	GEMOX v Observation
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5183
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.3

Statistical analysis title	RFS R1
Comparison groups	GEMOX v Observation

Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6772
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	1.97

### Secondary: Relapse-free survival (prognostic primary tumor location)

End point title	Relapse-free survival (prognostic primary tumor location)
End point description:	
End point type	Secondary
End point timeframe:	
up to 5.5 years	

End point values	GEMOX	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95 <sup>[5]</sup>	99 <sup>[6]</sup>		
Units: month				
median (confidence interval 95%)				
Intrahepatic	30.4 (12.9 to 45.8)	12.6 (8.3 to 38.2)		
Extrahepatic	38.7 (21.0 to 75)	15.9 (12.3 to 32.9)		
Gallbladder	11.5 (6.0 to 60)	62 (11.5 to 78)		

Notes:

[5] - Intrahepatic (41), extrahepatic (37), gallbladder (17)

[6] - Intrahepatic (45), extrahepatic (33), gallbladder (21)

### Statistical analyses

<b>Statistical analysis title</b>	RFS intrahepatic
Comparison groups	GEMOX v Observation
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2004
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.72

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	1.2

<b>Statistical analysis title</b>	RFS extrahepatic
Comparison groups	GEMOX v Observation
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0854
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	1.08

<b>Statistical analysis title</b>	RFS gallbladder
Comparison groups	GEMOX v Observation
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0345
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	2.559
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.04
upper limit	6.32

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Overall period of the study (up to 5.5 years after randomization)

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	11.0
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### Reporting groups

Reporting group title	GEMOX
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Reporting group description:

The GEMOX regimen consisted by the administration of Gemcitabine Hydrochloride and Oxaliplatin in cycle of two days:

- Gemcitabine Hydrochloride was administered at the dose of 1000mg/m<sup>2</sup> intravenously in 500 mL NaCl 0.9% over 100 minutes (fixed-dose infusion rate, 10 mg/m<sup>2</sup>/min) on Day 1 (D1).

- Oxaliplatin was administered at the dose of 85 mg/m<sup>2</sup> intravenously in 500 mL glucose 5% over 2 hours on D2.

GEMOX was administrated every 14 days for 12 cycles to the patients who met all inclusion criteria, none of the exclusion criteria and were randomized in arm A.

Reporting group title	Observation
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Reporting group description: -

Serious adverse events	GEMOX	Observation	
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 95 (23.16%)	13 / 99 (13.13%)	
number of deaths (all causes)	41	41	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Chronic myeloid leukaemia			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	1 / 95 (1.05%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peptic ulcer haemorrhage			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	1 / 95 (1.05%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
fever			
subjects affected / exposed	1 / 95 (1.05%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumopathy			
subjects affected / exposed	1 / 95 (1.05%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress syndrome adult			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Investigations			
Biopsy liver			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
alternative dictionary used: MedDRA 16.0			



subjects affected / exposed	0 / 95 (0.00%)	2 / 99 (2.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femoral neck fracture			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	1 / 95 (1.05%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	1 / 95 (1.05%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Cardio-respiratory arrest			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction acute			
subjects affected / exposed	1 / 95 (1.05%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Neurotoxicity NOS			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	1 / 95 (1.05%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
alternative dictionary used: MedDRA 14.0			

subjects affected / exposed	1 / 95 (1.05%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 95 (1.05%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	1 / 95 (1.05%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 95 (1.05%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 95 (1.05%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary anastomosis stenosis			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis intrahepatic			
alternative dictionary used: MedDRA 16.0			

subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Urticaria			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	1 / 95 (1.05%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Biliary sepsis			
alternative dictionary used: MedDRA 16			
subjects affected / exposed	1 / 95 (1.05%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary tract infection			
subjects affected / exposed	1 / 95 (1.05%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	2 / 95 (2.11%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis infective			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	1 / 95 (1.05%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
alternative dictionary used: MedDRA 14.0			

subjects affected / exposed	1 / 95 (1.05%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prosthesis related infection alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	1 / 95 (1.05%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septicemia due to Escherichia coli (E. coli)			
subjects affected / exposed	2 / 95 (2.11%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septicaemia alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 95 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	GEMOX	Observation	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	93 / 95 (97.89%)	64 / 99 (64.65%)	
Cardiac disorders			
Oedema			
subjects affected / exposed	5 / 95 (5.26%)	1 / 99 (1.01%)	
occurrences (all)	7	1	
Nervous system disorders			

Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	76 / 95 (80.00%) 136	5 / 99 (5.05%) 8	
Taste alteration subjects affected / exposed occurrences (all)	12 / 95 (12.63%) 15	0 / 99 (0.00%) 0	
Headache subjects affected / exposed occurrences (all)	12 / 95 (12.63%) 17	2 / 99 (2.02%) 3	
Blood and lymphatic system disorders			
Haemoglobin subjects affected / exposed occurrences (all)	76 / 95 (80.00%) 128	24 / 99 (24.24%) 41	
Neutrophil count subjects affected / exposed occurrences (all)	67 / 95 (70.53%) 96	6 / 99 (6.06%) 15	
Platelet count subjects affected / exposed occurrences (all)	87 / 95 (91.58%) 136	24 / 99 (24.24%) 41	
Leukocyte subjects affected / exposed occurrences (all)	44 / 95 (46.32%) 63	9 / 99 (9.09%) 17	
Infections and infestations			
Infection subjects affected / exposed occurrences (all)	14 / 95 (14.74%) 18	4 / 99 (4.04%) 7	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 December 2009	In the first version of the protocol, the platelets values for dose adjustment in the event of hematological or non-hematological toxicities (neuropathy excluded) during intercur was $10\,000 \leq \text{Plaquettes} < 75\,000/\text{mm}^3$ . It was then modified to $25\,000\,000 \leq \text{Platelets} < 75\,000/\text{mm}^3$ .
03 March 2011	Coagulation was added to the list of biological exams at baseline.
06 May 2011	To adapt to a recurring clinical situation where patients had a delay in treatment administration due to a grade 2 adverse event even though they presented no symptoms, the treatment was permanently discontinued if the postponement of treatment was greater than 28 days (6 weeks) rather than 21 days (5 weeks).

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

When the trial was designed in 2009, gemcitabine-oxaliplatin combination was considered a valuable regimen for advanced disease. Nowadays, the reference first-line regimen in the advanced setting gemcitabine-cisplatin combination.

Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/30707660>

<http://www.ncbi.nlm.nih.gov/pubmed/35182925>