# 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 |

### 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 |
| Scientific contact | Nourredine AIT-RAHMOUNE, Unicancer, 33 1 71 93 67 04, n.ait-rahmoune@unicancer.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 | 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 Prodige 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 |
| **Arm title** | 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/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

| | |
|---|---|
| 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/m2 intravenously in 500 mL NaCl 0.9% over 100 minutes (fixed-dose infusion rate, 10 mg/m2/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/m2 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.

| | |
|---|---|
| **Arm title** | Observation |

Arm description: -

| | |
|---|---|
| Arm type | No intervention |

No investigational medicinal product assigned in this arm

| **Number of subjects in period 1** | 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 |

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: -

| Reporting group values | GEMOX | Observation | Total |
|---|---|---|---|
| Number of subjects | 95 | 99 | 194 |
| Age categorical<br>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<br>Units: years | | | |
| median | 63 | 63 | |
| full range (min-max) | 33 to 83 | 40 to 80 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 38 | 49 | 87 |
| Male | 57 | 50 | 107 |
| Tumor localization<br>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 |
|---|---|

End point description:

| End point type | Primary |
|---|---|

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 |
|---|---|

End point description:

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

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

| **Statistical analysis title** | 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[1] | 99[2] | | |
| 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**

| **Statistical analysis title** | 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 |

| **Statistical analysis title** | 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 |

| **Statistical analysis title** | 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) |
| 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[3] | 99[4] | | |
| 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[5] | 99[6] | | |
| 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

| Statistical analysis title | 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 |

| **Statistical analysis title** | 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 |

| **Statistical analysis title** | 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 |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 11.0 |

### 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: -

| 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 %

| **Non-serious adverse events** | 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 | 76 / 95 (80.00%) | 5 / 99 (5.05%) | |
| occurrences (all) | 136 | 8 | |
| Taste alteration | | | |
| subjects affected / exposed | 12 / 95 (12.63%) | 0 / 99 (0.00%) | |
| occurrences (all) | 15 | 0 | |
| Headache | | | |
| subjects affected / exposed | 12 / 95 (12.63%) | 2 / 99 (2.02%) | |
| occurrences (all) | 17 | 3 | |
| Blood and lymphatic system disorders | | | |
| Haemoglobin | | | |
| subjects affected / exposed | 76 / 95 (80.00%) | 24 / 99 (24.24%) | |
| occurrences (all) | 128 | 41 | |
| Neutrophil count | | | |
| subjects affected / exposed | 67 / 95 (70.53%) | 6 / 99 (6.06%) | |
| occurrences (all) | 96 | 15 | |
| Platelet count | | | |
| subjects affected / exposed | 87 / 95 (91.58%) | 24 / 99 (24.24%) | |
| occurrences (all) | 136 | 41 | |
| Leukocyte | | | |
| subjects affected / exposed | 44 / 95 (46.32%) | 9 / 99 (9.09%) | |
| occurrences (all) | 63 | 17 | |
| Infections and infestations | | | |
| Infection | | | |
| subjects affected / exposed | 14 / 95 (14.74%) | 4 / 99 (4.04%) | |
| occurrences (all) | 18 | 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 intercure was 10 000 ≤ Plaquettes < 75 000/mm3. It was then modified to 25 000 000 ≤ Platelets < 75 000/mm3. |
| 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 discontinuted if the postponement of treatment was greater than 28 days (6 weeks) rather than 21 days (5 weeks). |

Notes:

### 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:

### Online references

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

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