# Clinical trial results:
# Randomized 1. Line treatment with gemcitabine, capecitabine, oxaliplatin vs gemcitabin and cisplatin to patients with cholangiocarcinoma.

## Summary

| | |
|---|---|
| EudraCT number | 2013-004854-46 |
| Trial protocol | DK |
| Global end of trial date | 01 May 2019 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 17 September 2020 |
| First version publication date | 17 September 2020 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | GI 1333 |

**Additional study identifiers**

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

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Herlev University Hospital, Department of Oncology |
| Sponsor organisation address | Herlev Ringvej 75, Herlev, Denmark, 2730 |
| Public contact | Oncology Department, Herlev University Hospital, 0045 38682329, ole.larsen@regionh.dk |
| Scientific contact | Oncology Department, Herlev University Hospital, 0045 38682329, ole.larsen@regionh.dk |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 30 August 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 01 May 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 01 May 2019 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

Progression free survival

Protection of trial subjects:

Patients that signed informed consent and fulfilling eligibility criteria were included. Continued monitoring of standard safety parameters during treatment.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 20 June 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 | Denmark: 100 |
| Worldwide total number of subjects | 100 |
| EEA total number of subjects | 100 |

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) | 47 |
| From 65 to 84 years | 52 |
| 85 years and over | 1 |

## Subject disposition

### Recruitment

Recruitment details:

The trial was opened for recruitment in June 2014 and closed for enrollment in November 2017 per protocol. Patients were included at 2 sites in Denmark.

### Pre-assignment

Screening details:

Eligible patients were 18 years or older with histopathological diagnosis of nonresectable, recurrent, or metastatic BTC or a cytologic diagnosis in combination with
radiological findings. Intrahepatic, perihilar, extrahepatic, and gallbladder cancers could be included—but not ampullary cancer. ECOG PS 0 or 1, bilirubin not above 2xULN.

### Pre-assignment period milestones

| | |
|---|---|
| Number of subjects started | 100 |
| Intermediate milestone: Number of subjects | pre-treatment: 100 |
| Number of subjects completed | 96 |

### Pre-assignment subject non-completion reasons

| | |
|---|---|
| Reason: Number of subjects | Protocol deviation: 2 |
| Reason: Number of subjects | rapid progression of disease: 2 |

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | CapOxGem |

Arm description:

Oxaliplatin and gemcitabine  every 2 weeks combined with continuos capecitabine

| | |
|---|---|
| Arm type | Experimental |
| 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:

oxaliplatin 50 mg/m2 every second week (infusion time of 30 min) until progression of disease

| | |
|---|---|
| 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:

gemcitabine 1000 mg/m2 every second week (infusion time of 30 min) until progression of disease

| | |
|---|---|
| Investigational medicinal product name | Capecitabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

capecitabine 650 mg/m2 twice-daily, continuously until progression of disease

| **Arm title** | CisGem |
|---|---|

Arm description:

Cisplatin and Gemcitabine on day 1 and 8 of each 3-week cycle, until progression of disease

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Cisplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

cisplatin 25 mg/m2 (infusion time of 60 min) on day 1 and day 8, repeated every 3 weeks until progression of disease (with restriction to accumulated dose of max 400 mg/m2)

| | |
|---|---|
| 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:

gemcitabine 1000 mg/m2 (infusion time of 30 min) on day 1 and day 8, repeated every 3 weeks until progression of disease

| **Number of subjects in period 1[1]** | CapOxGem | CisGem |
|---|---|---|
| Started | 47 | 49 |
| Completed | 41 | 38 |
| Not completed | 6 | 11 |
| Adverse event, serious fatal | - | 1 |
| Physician decision | - | 1 |
| Adverse event, non-fatal | 4 | 7 |
| early death | 2 | 2 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 4 patient did not complete pre-treatment period

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | CapOxGem |
| Reporting group description: | |
| Oxaliplatin and gemcitabine  every 2 weeks combined with continuos capecitabine | |
| Reporting group title | CisGem |
| Reporting group description: | |
| Cisplatin and Gemcitabine on day 1 and 8 of each 3-week cycle, until progression of disease | |

| Reporting group values | CapOxGem | CisGem | Total |
|---|---|---|---|
| Number of subjects | 47 | 49 | 96 |
| Age categorical<br>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) | | | 0 |
| From 65-84 years | | | 0 |
| 85 years and over | | | 0 |
| Age continuous<br>Units: years | | | |
| median | 65 | 65 | |
| full range (min-max) | 21 to 85 | 39 to 82 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 24 | 26 | 50 |
| Male | 23 | 23 | 46 |
| ECOG performance status<br>Units: Subjects | | | |
| ECOG PS 0 | 23 | 23 | 46 |
| ECOG PS 1 | 24 | 26 | 50 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | CapOxGem |
| Reporting group description: | |
| Oxaliplatin and gemcitabine  every 2 weeks combined with continuos capecitabine | |
| Reporting group title | CisGem |
| Reporting group description: | |
| Cisplatin and Gemcitabine on day 1 and 8 of each 3-week cycle, until progression of disease | |

### Primary: Progression free Survival

| | |
|---|---|
| End point title | Progression free Survival[1] |
| End point description: | |
| | |
| End point type | Primary |
| End point timeframe: | |
| Scans were performed every 12 weeks until progression of disease | |
| 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.<br>Justification: Sample size to small to compare the groups. | |

| End point values | CapOxGem | CisGem | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 | 49 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 5.7 (3.0 to 7.8) | 7.3 (6.0 to 8.7) | | |

### 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: | |
| time from randomisation to death (censoring at database lock Aug 2019) | |

| End point values | CapOxGem | CisGem | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 | 49 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 8.7 (6.5 to 11.2) | 12.0 (8.3 to 16.7) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Tumor response

| End point title | Tumor response |
|---|---|

End point description:

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

End point timeframe:

Tumor assessments were performed every 12 weeks during treatment

| End point values | CapOxGem | CisGem | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 | 49 | | |
| Units: subjects | | | | |
| Complete Response | 0 | 0 | | |
| Partial Response | 8 | 8 | | |
| Stable Disease | 20 | 31 | | |
| Progression | 14 | 5 | | |
| Not assessable | 5 | 5 | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| From date of first treatment to 28 days after last treatment with the trial | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | NCI-CTCAE |
| Dictionary version | 4 |

| Reporting groups | |
|---|---|
| Reporting group title | CapOxGem |
| Reporting group description: | |
| Oxaliplatin and gemcitabine every 2 weeks combined with continuos capecitabine | |
| Reporting group title | CisGem |
| Reporting group description: | |
| Cisplatin and Gemcitabine on day 1 and 8 of each 3-week cycle, until progression of disease | |

| Serious adverse events | CapOxGem | CisGem | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 16 / 47 (34.04%) | 19 / 49 (38.78%) | |
| number of deaths (all causes) | 44 | 46 | |
| number of deaths resulting from adverse events | 0 | 2 | |
| Vascular disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 2 / 47 (4.26%) | 6 / 49 (12.24%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 1 / 49 (2.04%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hypotension | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 49 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 49 (2.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombotic microangiopathy | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 49 (2.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Fever | | | |
| subjects affected / exposed | 2 / 47 (4.26%) | 2 / 49 (4.08%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Allergic reaction | Additional description: patient in CapOxGem - allergic reaction to oxaliplatin patient in CisGem- allergic reaction to concomitant medication (not study treatment) | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 12 / 49 (24.49%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 2 / 49 (4.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | Additional description: as symptom for COPD exacerbation | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 49 (2.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 49 (2.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| C-reactive protein increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 49 (2.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 49 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Cardiotoxicity | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 49 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 49 (2.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericardial effusion | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 49 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | Additional description: Non-STEMI | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 49 (2.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Seizure | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 49 (2.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 49 (2.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| stroke | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 1 / 49 (2.04%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 49 (2.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Oral hemorrhage | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 49 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 47 (6.38%) | 1 / 49 (2.04%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 2 / 47 (4.26%) | 0 / 49 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 49 (2.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hepatorenal syndrome | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 49 (2.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Renal and urinary disorders | | | |
| ureteral stones | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 49 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Infection | Additional description: Summarised term Infection, includes cases of biliary tract infection, gasteroentritis, infection with unknow focus, pancreatitis, urinary tract infection | | |
| subjects affected / exposed | 3 / 47 (6.38%) | 5 / 49 (10.20%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 3 / 47 (6.38%) | 0 / 49 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacteraemia | | | |
| subjects affected / exposed | 2 / 47 (4.26%) | 0 / 49 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 49 (2.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abscess | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 2 / 49 (4.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| hyperglycemia | | | |
| subjects affected / exposed | 2 / 47 (4.26%) | 1 / 49 (2.04%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 49 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | CapOxGem | CisGem | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed | 47 / 47 (100.00%) | 49 / 49 (100.00%) | |
| Investigations<br>Neutropenia<br>subjects affected / exposed<br>occurrences (all) | 4 / 47 (8.51%)<br>4 | 30 / 49 (61.22%)<br>30 | |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all) | 10 / 47 (21.28%)<br>10 | 16 / 49 (32.65%)<br>16 | |
| Vascular disorders<br>Thromoembolic event<br>subjects affected / exposed<br>occurrences (all) | 7 / 47 (14.89%)<br>7 | 12 / 49 (24.49%)<br>12 | |
| Nervous system disorders<br>Neuropathy peripheral<br>subjects affected / exposed<br>occurrences (all) | 41 / 47 (87.23%)<br>41 | 24 / 49 (48.98%)<br>24 | |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all) | 10 / 47 (21.28%)<br>10 | 17 / 49 (34.69%)<br>17 | |
| Febrile neutropenia<br>subjects affected / exposed<br>occurrences (all) | 0 / 47 (0.00%)<br>0 | 5 / 49 (10.20%)<br>5 | |
| General disorders and administration site conditions<br>Fatigue<br>subjects affected / exposed<br>occurrences (all) | 37 / 47 (78.72%)<br>37 | 36 / 49 (73.47%)<br>36 | |
| Ear and labyrinth disorders | | | |

| | | | |
|---|---|---|---|
| Tinnitus | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 10 / 49 (20.41%) | |
| occurrences (all) | 1 | 10 | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 35 / 47 (74.47%) | 34 / 49 (69.39%) | |
| occurrences (all) | 35 | 34 | |
| Vomiting | | | |
| subjects affected / exposed | 20 / 47 (42.55%) | 15 / 49 (30.61%) | |
| occurrences (all) | 20 | 15 | |
| Diarrhoea | | | |
| subjects affected / exposed | 19 / 47 (40.43%) | 9 / 49 (18.37%) | |
| occurrences (all) | 19 | 9 | |
| Hepatobiliary disorders | | | |
| Biliary tract disorder | | | |
| subjects affected / exposed | 9 / 47 (19.15%) | 2 / 49 (4.08%) | |
| occurrences (all) | 9 | 2 | |
| Skin and subcutaneous tissue disorders | | | |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 20 / 47 (42.55%) | 0 / 49 (0.00%) | |
| occurrences (all) | 20 | 0 | |
| Infections and infestations | | | |
| Infection | | | |
| subjects affected / exposed | 33 / 47 (70.21%) | 40 / 49 (81.63%) | |
| occurrences (all) | 33 | 40 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 30 June 2015 | In treatment arm CisGem, the treatment with Cisplatin was limited to an accumulated dose of max 400 mg/m2 |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

### Online references

http://www.ncbi.nlm.nih.gov/pubmed/32698410