# Clinical trial results:
# A MULTINATIONAL, RANDOMIZED, PHASE II STUDY OF THE COMBINATION OF NAB-PACLITAXEL AND GEMCITABINE WITH OR WITHOUT IL-6R INHIBITOR, TOCILIZUMAB, AS FIRST-LINE TREATMENT IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC PANCREATIC CANCER.

## Summary

| | |
|---|---|
| EudraCT number | 2016-000643-13 |
| Trial protocol | DK NO |
| Global end of trial date | 18 July 2022 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 22 July 2023 |
| First version publication date | 22 July 2023 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | GI1612 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02767557 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Herlev & Gentofte Hospital, Department of Oncology |
| Sponsor organisation address | Borgmester Ib Juuls Vej 1, Herlev, Denmark, 2730 |
| Public contact | Inna Chen, Herlev & Gentofte Hospital, +45 38682898, inna.chen@regionh.dk |
| Scientific contact | Inna Chen, Herlev & Gentofte Hospital, +45 38682898, inna.chen@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 | 09 January 2023 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 18 July 2022 |
| Global end of trial reached? | Yes |
| Global end of trial date | 18 July 2022 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To compare overall survival at 6 months of gemcitabine/nab-paclitaxel plus tocilizumab and gemcitabine/nab-paclitaxel.

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 | 31 January 2017 |
| 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 | Norway: 1 |
| Country: Number of subjects enrolled | Denmark: 146 |
| Worldwide total number of subjects | 147 |
| EEA total number of subjects | 147 |

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) | 62 |
| From 65 to 84 years | 85 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

The trial was opened for recruitment in January 2017 and closed for enrollment in July 2021 . Patients were included at 2 sites, Copenhagen University Hospital - Herlev and Gentofte in Denmark and Oslo University Hospital, Norway.

### Pre-assignment

Screening details:

Eligible patients were ≥ 18 years with locally advanced or metastatic pancreatic cancer, who had not previously received treatment in the advanced setting, ECOG PS 0-1, mGPS >=1, with measureable disease and adequate organ and hematologic function.

### Period 1

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

Blinding implementation details:

Prior to randomised portion of the trial, a safety cohort of 6 participants recieved experimental treatment (unrandomised). 141 participants were randomly assigned to experimental and standard treatment, stratification by ECOG PS (0 vs 1) and stage of disease (locally advanced vs metastatic.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Safety Cohort |

Arm description:

Gemcitabine and nab-paclitaxel in combination with tocilizumab.
Treatment continued until disease progression, unacceptable toxicity, pregnancy, patient’s withdrawal of the informed consent at his/hers own request or investigator’s discretion

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

Dosage and administration details:

1000 mg/m² i.v. on day 1, day 8 and day 15 of every 28 day cycle.

| | |
|---|---|
| Investigational medicinal product name | nab-paclitaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

125 mg/m² i.v. on day 1, day 8 and day 15 of every 28 day cycle.

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

Dosage and administration details:

8 mg/kg given i.v. on day 1 of every 28 day cycle.

| | |
|---|---|
| **Arm title** | Gem/Nab/Toc |

Arm description:

Gemcitabine and nab-paclitaxel in combination with tocilizumab.
Treatment continued until disease progression, unacceptable toxicity, pregnancy, patient's withdrawal of the informed consent at his/hers own request or investigator's discretion

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

Dosage and administration details:

1000 mg/m² i.v. on day 1, day 8 and day 15 of every 28 day cycle.

| | |
|---|---|
| Investigational medicinal product name | nab-paclitaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

125 mg/m² i.v. on day 1, day 8 and day 15 of every 28 day cycle.

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

Dosage and administration details:

8 mg/kg given i.v. on day 1 of every 28 day cycle.

| | |
|---|---|
| **Arm title** | Gem/Nab |

Arm description:

Gemcitabine and nab-paclitaxel
Treatment continued until disease progression, unacceptable toxicity, pregnancy, patient's withdrawal of the informed consent at his/hers own request or investigator's discretion

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

Dosage and administration details:

1000 mg/m² i.v. on day 1, day 8 and day 15 of every 28 day cycle.

| | |
|---|---|
| Investigational medicinal product name | nab-paclitaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

125 mg/m² i.v. on day 1, day 8 and day 15 of every 28 day cycle.

| **Number of subjects in period 1** | Safety Cohort | Gem/Nab/Toc | Gem/Nab |
|---|---|---|---|
| Started | 6 | 70 | 71 |
| Completed | 5 | 47 | 53 |
| Not completed | 1 | 23 | 18 |
| Adverse event, serious fatal | - | 4 | 2 |
| Consent withdrawn by subject | - | 2 | 5 |
| Physician decision | - | 2 | 1 |
| Adverse event, non-fatal | - | 9 | 6 |
| Death from disease under study | 1 | 4 | 3 |
| Resection of tumor | - | 2 | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Safety Cohort |
| Reporting group description: | |
| Gemcitabine and nab-paclitaxel in combination with tocilizumab.<br>Treatment continued until disease progression, unacceptable toxicity, pregnancy, patient's withdrawal of the informed consent at his/hers own request or investigator's discretion | |
| Reporting group title | Gem/Nab/Toc |
| Reporting group description: | |
| Gemcitabine and nab-paclitaxel in combination with tocilizumab.<br>Treatment continued until disease progression, unacceptable toxicity, pregnancy, patient's withdrawal of the informed consent at his/hers own request or investigator's discretion | |
| Reporting group title | Gem/Nab |
| Reporting group description: | |
| Gemcitabine and nab-paclitaxel<br>Treatment continued until disease progression, unacceptable toxicity, pregnancy, patient's withdrawal of the informed consent at his/hers own request or investigator's discretion | |

| Reporting group values | Safety Cohort | Gem/Nab/Toc | Gem/Nab |
|---|---|---|---|
| Number of subjects | 6 | 70 | 71 |
| Age categorical<br>Units: Subjects | | | |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over | | | |
| Age continuous<br>Units: years | | | |
| median | 69.5 | 68 | 67 |
| full range (min-max) | 49 to 76 | 34 to 84 | 36 to 84 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 3 | 30 | 28 |
| Male | 3 | 40 | 43 |
| ECOG Performance status<br>Units: Subjects | | | |
| ECOG PS 0 | 2 | 26 | 27 |
| ECOG PS 1 | 4 | 44 | 44 |
| Disease Stage<br>Units: Subjects | | | |
| Locally advanced | 0 | 5 | 6 |
| Metastatic | 6 | 65 | 65 |

| Reporting group values | Total | | |
|---|---|---|---|
| Number of subjects | 147 | | |
| 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 | | | |
| full range (min-max) | - | | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 61 | | |
| Male | 86 | | |
| ECOG Performance status<br>Units: Subjects | | | |
| ECOG PS 0 | 55 | | |
| ECOG PS 1 | 92 | | |
| Disease Stage<br>Units: Subjects | | | |
| Locally advanced | 11 | | |
| Metastatic | 136 | | |

**Subject analysis sets**

| | |
|---|---|
| Subject analysis set title | Efficacy analysis |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

Patients randomised to either Gem/Nab/Toc or Gem/Nab and recieved at treatment at least once

| | |
|---|---|
| Subject analysis set title | Safety |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

Both the patients that were included in the safety cohort (Gem/Nab/Toc) and those randomised to either Gem/Nab/Toc or Gem/Nab and having received treatment at least once.

| Reporting group values | Efficacy analysis | Safety | |
|---|---|---|---|
| Number of subjects | 141 | 147 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |

| | | | |
|---|---|---|---|
| Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over | | | |
| Age continuous<br>Units: years | | | |
| median | 67 | 67 | |
| full range (min-max) | 34 to 84 | 34 to 84 | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 58 | 61 | |
| Male | 83 | 86 | |
| ECOG Performance status<br>Units: Subjects | | | |
| ECOG PS 0 | 53 | 55 | |
| ECOG PS 1 | 88 | 92 | |
| Disease Stage<br>Units: Subjects | | | |
| Locally advanced | 11 | 11 | |
| Metastatic | 130 | 136 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Safety Cohort |

Reporting group description:

Gemcitabine and nab-paclitaxel in combination with tocilizumab.
Treatment continued until disease progression, unacceptable toxicity, pregnancy, patient's withdrawal of the informed consent at his/hers own request or investigator's discretion

| | |
|---|---|
| Reporting group title | Gem/Nab/Toc |

Reporting group description:

Gemcitabine and nab-paclitaxel in combination with tocilizumab.
Treatment continued until disease progression, unacceptable toxicity, pregnancy, patient's withdrawal of the informed consent at his/hers own request or investigator's discretion

| | |
|---|---|
| Reporting group title | Gem/Nab |

Reporting group description:

Gemcitabine and nab-paclitaxel
Treatment continued until disease progression, unacceptable toxicity, pregnancy, patient's withdrawal of the informed consent at his/hers own request or investigator's discretion

| | |
|---|---|
| Subject analysis set title | Efficacy analysis |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

Patients randomised to either Gem/Nab/Toc or Gem/Nab and recieved at treatment at least once

| | |
|---|---|
| Subject analysis set title | Safety |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

Both the patients that were included in the safety cohort (Gem/Nab/Toc) and those randomised to either Gem/Nab/Toc or Gem/Nab and having received treatment at least once.

### Primary: OS rate at 6 months

| | |
|---|---|
| End point title | OS rate at 6 months[1] |

End point description:

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

End point timeframe:

6 months from randomisation

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Safety cohort of 6 patients is not included in the efficacy endpoint, which was analysed in for patients in the randomised part of the trial

| End point values | Gem/Nab/Toc | Gem/Nab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 70 | 71 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 68.6 (56.3 to 78.1) | 62 (49.6 to 72.1) | | |

## Statistical analyses

| **Statistical analysis title** | Comparison of OS rate at specific timepoint |
|---|---|
| Comparison groups | Gem/Nab/Toc v Gem/Nab |
| Number of subjects included in analysis | 141 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.409 |
| Method | z-test |

## Secondary: Overall Survival

| End point title | Overall Survival[2] |
|---|---|

End point description:

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

End point timeframe:

Time from randomisation to death

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Safety cohort of 6 patients is not included in the efficacy endpoint, which was analysed in for patients in the randomised part of the trial

| **End point values** | Gem/Nab/Toc | Gem/Nab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 70 | 71 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 8.4 (6.7 to 11.4) | 8.0 (5.9 to 9.8) | | |

### Statistical analyses

| **Statistical analysis title** | Overall survival |
|---|---|
| Comparison groups | Gem/Nab/Toc v Gem/Nab |
| Number of subjects included in analysis | 141 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.096 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.75 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.54 |
| upper limit | 1.05 |

## Secondary: Progression free survival

| End point title | Progression free survival[3] |
|---|---|

End point description:

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

End point timeframe:

time from randomisation to radiological progression or death

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Safety cohort of 6 patients is not included in the efficacy endpoint, which was analysed in for patients in the randomised part of the trial

| End point values | Gem/Nab/Toc | Gem/Nab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 70 | 71 | | |
| Units: month | | | | |
| median (confidence interval 95%) | 5.6 (3.9 to 7.4) | 5.5 (3.5 to 7.0) | | |

### Statistical analyses

| Statistical analysis title | PFS |
|---|---|
| Comparison groups | Gem/Nab/Toc v Gem/Nab |
| Number of subjects included in analysis | 141 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.339 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.85 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.6 |
| upper limit | 1.19 |

## Secondary: Objective response rate

| End point title | Objective response rate[4] |
|---|---|

End point description:

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

End point timeframe:

tumor assessment every 8 weeks from treatment start

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Safety cohort of 6 patients is not included in the efficacy endpoint, which was analysed in for patients in the randomised part of the trial

| End point values | Gem/Nab/Toc | Gem/Nab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 70 | 71 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 37.1 (25.9 to 45.9) | 35.2 (24.2 to 47.5) | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| Time from treatment start to 30 days after last treatment | |
| Adverse event reporting additional description: | |
| For non-serious AE section, only AEs with causal relationship to treatment (AR) are listed (numbers includes subjects/occurences reported as SARs as well). | |
| Assessment type | Systematic |

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

| Reporting groups | |
|---|---|
| Reporting group title | Safety Cohort |
| Reporting group description: | |
| Gemcitabine and nab-paclitaxel in combination with tocilizumab.<br>Treatment continued until disease progression, unacceptable toxicity, pregnancy, patient's withdrawal of the informed consent at his/hers own request or investigator's discretion | |
| Reporting group title | Gem/Nab/Toc |
| Reporting group description: | |
| Gemcitabine and nab-paclitaxel in combination with tocilizumab.<br>Treatment continued until disease progression, unacceptable toxicity, pregnancy, patient's withdrawal of the informed consent at his/hers own request or investigator's discretion | |
| Reporting group title | Gem/Nab |
| Reporting group description: | |
| Gemcitabine and nab-paclitaxel<br>Treatment continued until disease progression, unacceptable toxicity, pregnancy, patient's withdrawal of the informed consent at his/hers own request or investigator's discretion | |

| Serious adverse events | Safety Cohort | Gem/Nab/Toc | Gem/Nab |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 49 / 70 (70.00%) | 40 / 71 (56.34%) |
| number of deaths (all causes) | 6 | 70 | 71 |
| number of deaths resulting from adverse events | 0 | 4 | 2 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 70 (2.86%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 70 (1.43%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombotic angiopathy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 70 (1.43%) | 0 / 71 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Portal vein thrombosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 70 (1.43%) | 0 / 71 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Capillary leak syndrome | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 70 (1.43%) | 0 / 71 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 70 (0.00%) | 3 / 71 (4.23%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| General disorders and administration site conditions | | | |
| Edema limbs | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 70 (2.86%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fever | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 70 (2.86%) | 2 / 71 (2.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| flu like symptoms | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 70 (0.00%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 70 (1.43%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 4 / 70 (5.71%) | 5 / 71 (7.04%) |
| occurrences causally related to treatment / all | 1 / 1 | 4 / 4 | 5 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 70 (1.43%) | 0 / 71 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 70 (1.43%) | 0 / 71 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 70 (0.00%) | 0 / 71 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Mania | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 70 (0.00%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anxiety | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 70 (0.00%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 70 (2.86%) | 0 / 71 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 70 (1.43%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 70 (0.00%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 70 (2.86%) | 0 / 71 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 70 (1.43%) | 0 / 71 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 70 (1.43%) | 0 / 71 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 70 (0.00%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Hepatic encephalopathy | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 70 (1.43%) | 0 / 71 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral infarction | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 70 (2.86%) | 3 / 71 (4.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 70 (2.86%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 4 / 70 (5.71%) | 3 / 71 (4.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 4 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Duodenal ulcer | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 70 (1.43%) | 0 / 71 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 7 / 70 (10.00%) | 3 / 71 (4.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 9 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 7 / 70 (10.00%) | 2 / 71 (2.82%) |
| occurrences causally related to treatment / all | 1 / 1 | 8 / 8 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ileus | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 70 (1.43%) | 0 / 71 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 70 (2.86%) | 0 / 71 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 70 (1.43%) | 0 / 71 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 3 / 70 (4.29%) | 3 / 71 (4.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 70 (2.86%) | 3 / 71 (4.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis intestinal perforated | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 70 (2.86%) | 0 / 71 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 70 (1.43%) | 3 / 71 (4.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 70 (0.00%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Gallbladder obstruction | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 70 (1.43%) | 0 / 71 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic failure | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 70 (1.43%) | 0 / 71 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 70 (1.43%) | 0 / 71 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Renal and urinary disorders | | | |

| | | | |
|---|---|---|---|
| Bladder spasm | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 70 (1.43%) | 0 / 71 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 70 (1.43%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematuria | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 70 (1.43%) | 0 / 71 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 70 (0.00%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 9 / 70 (12.86%) | 7 / 71 (9.86%) |
| occurrences causally related to treatment / all | 1 / 1 | 10 / 12 | 5 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 15 / 70 (21.43%) | 7 / 71 (9.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 14 / 19 | 5 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 2 / 2 | 1 / 1 |
| Infection unknown focus | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 3 / 70 (4.29%) | 5 / 71 (7.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | 7 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 70 (1.43%) | 0 / 71 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Abscess | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 5 / 70 (7.14%) | 2 / 71 (2.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 6 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 70 (1.43%) | 0 / 71 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 70 (2.86%) | 2 / 71 (2.82%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Biliary tract infection | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 70 (2.86%) | 2 / 71 (2.82%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| infection due to necrosis/liver infarct | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 70 (1.43%) | 0 / 71 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 70 (1.43%) | 0 / 71 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epididymitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 70 (1.43%) | 0 / 71 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 70 (1.43%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium difficile infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 70 (0.00%) | 4 / 71 (5.63%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 4 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 70 (0.00%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary candida infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 70 (0.00%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 70 (0.00%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Ketosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 70 (1.43%) | 0 / 71 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 70 (0.00%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acidosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 70 (0.00%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| **Non-serious adverse events** | Safety Cohort | Gem/Nab/Toc | Gem/Nab |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 6 / 6 (100.00%) | 70 / 70 (100.00%) | 71 / 71 (100.00%) |
| Investigations | | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 54 / 70 (77.14%) | 35 / 71 (49.30%) |
| occurrences (all) | 10 | 292 | 124 |
| Neutropenia | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | 51 / 70 (72.86%) | 29 / 71 (40.85%) |
| occurrences (all) | 10 | 212 | 75 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 37 / 70 (52.86%) | 17 / 71 (23.94%) |
| occurrences (all) | 6 | 71 | 30 |
| Nervous system disorders | | | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 5 / 6 (83.33%) | 46 / 70 (65.71%) | 46 / 71 (64.79%) |
| occurrences (all) | 13 | 113 | 100 |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 22 / 70 (31.43%) | 16 / 71 (22.54%) |
| occurrences (all) | 7 | 46 | 33 |
| Dizziness | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 70 (2.86%) | 4 / 71 (5.63%) |
| occurrences (all) | 2 | 2 | 9 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 48 / 70 (68.57%) | 45 / 71 (63.38%) |
| occurrences (all) | 7 | 150 | 104 |
| Fever | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 4 / 70 (5.71%) | 10 / 71 (14.08%) |
| occurrences (all) | 2 | 6 | 19 |
| flu/flu like symptoms | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 5 / 70 (7.14%) | 6 / 71 (8.45%) |
| occurrences (all) | 1 | 5 | 6 |
| Oedema | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 29 / 70 (41.43%) | 17 / 71 (23.94%) |
| occurrences (all) | 5 | 68 | 35 |
| Pain | Additional description: Includes different verbatims such as pain + abdominal | | |

| | | | |
|---|---|---|---|
| | pain+ pain in extremity+ chest wall pain | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 11 / 70 (15.71%) | 5 / 71 (7.04%) |
| occurrences (all) | 2 | 16 | 5 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 7 / 70 (10.00%) | 12 / 71 (16.90%) |
| occurrences (all) | 2 | 9 | 27 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 6 / 70 (8.57%) | 3 / 71 (4.23%) |
| occurrences (all) | 1 | 6 | 3 |
| Immune system disorders | | | |
| Allergic reaction | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 2 / 70 (2.86%) | 3 / 71 (4.23%) |
| occurrences (all) | 3 | 5 | 3 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | 44 / 70 (62.86%) | 45 / 71 (63.38%) |
| occurrences (all) | 14 | 102 | 91 |
| Nausea | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 41 / 70 (58.57%) | 41 / 71 (57.75%) |
| occurrences (all) | 4 | 90 | 79 |
| Vomiting | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 22 / 70 (31.43%) | 21 / 71 (29.58%) |
| occurrences (all) | 2 | 35 | 30 |
| Haemorrhage | Additional description: Includes different types of hemorrhage; mostly as GI but also vaginal , hematuria, epsitaxis, subconjunctiva | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 8 / 70 (11.43%) | 6 / 71 (8.45%) |
| occurrences (all) | 3 | 11 | 7 |
| Mucositis | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | 20 / 70 (28.57%) | 14 / 71 (19.72%) |
| occurrences (all) | 10 | 34 | 22 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 7 / 70 (10.00%) | 7 / 71 (9.86%) |
| occurrences (all) | 1 | 8 | 12 |
| Dyspnoea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 3 / 70 (4.29%) | 5 / 71 (7.04%) |
| occurrences (all) | 0 | 4 | 7 |
| Skin and subcutaneous tissue disorders | | | |
| Nail ridging | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 4 / 70 (5.71%) | 4 / 71 (5.63%) |
| occurrences (all) | 4 | 6 | 9 |
| Rash | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 12 / 70 (17.14%) | 12 / 71 (16.90%) |
| occurrences (all) | 1 | 22 | 15 |
| Infections and infestations | | | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 11 / 70 (15.71%) | 5 / 71 (7.04%) |
| occurrences (all) | 0 | 14 | 5 |
| Infection | Additional description: includes infections of unknown focus, Pneumonia, Urinary tract, Clostridium difficile, Upper Respiratory tract, Pulmonary candida, Biliary tract , Cholecystitis, groin, Epididymitis, Herpes, Eye, Nail , Erysipelas, Skin, Wound ,foot | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 28 / 70 (40.00%) | 28 / 71 (39.44%) |
| occurrences (all) | 7 | 55 | 43 |
| Metabolism and nutrition disorders | | | |
| Anorexia | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 31 / 70 (44.29%) | 32 / 71 (45.07%) |
| occurrences (all) | 5 | 53 | 60 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 70 (0.00%) | 4 / 71 (5.63%) |
| occurrences (all) | 0 | 0 | 5 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 17 October 2016 | Additional laboratory test for lipid profile at start of each cycle.<br>Addiotnal tumor biopsy at time of progression (if feasible and at the discretion of investigator) |
| 01 May 2018 | - Additional center at Oslo University Hospital<br>- additional exploratory objective and endpoints were added to assess whether inhibition of IL-6R has an impact on cachexia in patients with locally advanced or metastatic pancreatic cancer<br>- Adjustment to study time lines |
| 04 December 2018 | After interim safety analysis - implementation of<br>Mandatory supportive treatment with G-CSF: In cycle 1 all patients will receive G-CSF (self-administrated) on day 9, i.e. 24 hours after administration of chemotherapy on day 8, or on day 8 in the clinic if self-administration is not an option.<br>Upon reference all PACTO patients must be admitted and if ANC < 1.0 x 109/L is observed, G-CSF and antibiotics (tazocin and metronidazole) will be initiated, regardless of fever or CRP. Antibiotics should be adjusted / discontinued dependent on clinic thereafter.<br>Additionally clarification anf corrections in the protocol base on comments from Norvegian Competent authority |
| 08 December 2019 | Adjustment of study timelines |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported