



Clinical trial results:

Phase II Study for the Evaluation of the Efficacy of Gemcitabine plus Erlotinib in Rash-positive Patients with Metastatic Pancreatic Cancer and Good Risk Factors

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2011-005471-17 |
| Trial protocol | DE |
| Global end of trial date | 01 February 2017 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 16 June 2018 |
| First version publication date | 16 June 2018 |

Trial information

Trial identification

| | |
|-----------------------|------|
| Sponsor protocol code | RASH |
|-----------------------|------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01729481 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Klinikum der Universität München-Großhadern |
| Sponsor organisation address | Marchioninstr. 15, München, Germany, 81377 |
| Public contact | Study office, Klinikum der Universität München-Großhadern, 49 89440072208, Matthias.Wolff@med.uni-muenchen.de |
| Scientific contact | Study office, Klinikum der Universität München-Großhadern, 49 89440072208, Matthias.Wolff@med.uni-muenchen.de |

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 | 16 August 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 01 February 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 01 February 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

1-year survival rate of "good risk" patients who develop rash under treatment with gemcitabine/erlotinib

Protection of trial subjects:

This clinical study was designed and implemented and reported in accordance with the International Conference on Harmonisation (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable European and national regulations (including European Directive 2001/20/EC and German Drug Law (AMG)) and with the ethical principles laid down in the Declaration of Helsinki. Participating subjects signed the informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision.

Background therapy:

Not applicable.

Evidence for comparator:

Not applicable.

| | |
|---|--------------|
| Actual start date of recruitment | 11 July 2012 |
| 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 | Germany: 150 |
| Worldwide total number of subjects | 150 |
| EEA total number of subjects | 150 |

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) | 88 |

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

Subject disposition

Recruitment

Recruitment details:

25 investigational sites in Germany were participating. 150 subjects were screened and enrolled at 20 of these 25 investigational sites.

The first patient was enrolled 11-July-2012, the last patient 6-July-2015.

Pre-assignment

Screening details:

Main inclusion criteria:

- Histologically confirmed metastatic adenocarcinoma of the pancreas (UICC stadium IV; any T, any N, M1 following TNM)
- At least one measurable tumor lesion (CT or MRI) according to RECIST version 1.1
- ECOG PS 0 and 1
- Between 18 and 75 years of age
- Bilirubin \leq 1.5 ULN (biliary stent permitted)

Pre-assignment period milestones

| | |
|------------------------------|-----|
| Number of subjects started | 150 |
| Number of subjects completed | 144 |

Pre-assignment subject non-completion reasons

| | |
|----------------------------|---|
| Reason: Number of subjects | Violation in-/exclusion criteria (retrospectively): 1 |
| Reason: Number of subjects | Death: 1 |
| Reason: Number of subjects | Progression of tumor disease: 1 |
| Reason: Number of subjects | Patient's wish: 1 |
| Reason: Number of subjects | Loss of contact: 1 |
| Reason: Number of subjects | Consent withdrawn by subject: 1 |

Period 1

| | |
|------------------------------|----------------------------------|
| Period 1 title | Run-in with Gemcitabin/Erlotinib |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|-----------|--------|
| Arm title | Run-in |
|-----------|--------|

Arm description:

Treatment with gemcitabine 1000 mg/m² BSA weekly and erlotinib, 100 mg once daily for 4 weeks. Treatment was discontinued earlier in case of progression of the metastatic pancreatic adenocarcinoma, unacceptable toxicity or other reasons (patient's wish, investigator's decision).

| | |
|--|----------------------------------|
| Arm type | Run-in |
| Investigational medicinal product name | Gemcitabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous drip use |

Dosage and administration details:

1000 mg/m² on D1, D8, D15, D21 of one 28-day cycle.

| | |
|--|---------------|
| Investigational medicinal product name | Erlotinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

100 mg once daily for 28 days.

| Number of subjects in period 1^[1] | Run-in |
|---|--------|
| Started | 144 |
| Completed | 116 |
| Not completed | 28 |
| Physician decision | 6 |
| Adverse event, non-fatal | 3 |
| Patient's wish | 7 |
| Death | 5 |
| Progression of tumor disease | 7 |

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: Sample size calculation of 150 patients included 10% drop-outs. As 6 patients were screening failures , 144 patients entered the Run-in phase.

Period 2

| | |
|------------------------------|---|
| Period 2 title | Treatment according to occurrence of rash |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-----------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Arm A (rash-positive) |

Arm description:

Patient who had developed skin rash after 4 weeks of treatment with gemcitabine 1000 mg/m² BSA weekly and erlotinib 100 mg p.o. once daily in the Run-in phase (first 4 treatment weeks), continued treatment with gemcitabine 1000 mg/m² weekly on D1, D7, D14 of each 28-day treatment cycle and erlotinib 100 mg p.o. once daily.

Treatment was continued until progression of the metastatic pancreatic adenocarcinoma, unacceptable toxicity or other reasons (patient's wish, investigator's decision).

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

Dosage and administration details:

1000 mg/m² BSA on D1, D8, D15 of each 28-day cycle

| | |
|---|-----------------------|
| Investigational medicinal product name | Erlotinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Coated tablet |
| Routes of administration | Oral use |
| Dosage and administration details: 100 mg once daily | |
| Arm title | Arm B (rash-negative) |

Arm description:

Patient who had developed no skin rash after 4 weeks of treatment with gemcitabine 1000 mg/m² BSA weekly and erlotinib 100 mg p.o. once daily in the Run-in phase (first 4 treatment weeks), received further treatment with FOLFIRINOX (fluorouracil, folinic acid, irinotecan, oxaliplatin). Treatment was continued until progression of the metastatic pancreatic adenocarcinoma, unacceptable toxicity or other reasons (patient's wish, investigator's decision). Only rash-negative patients who were given FOLFIRINOX treatment after Run-in are included.

| | |
|--|--|
| Arm type | treatment choice for RASH-negative patients |
| Investigational medicinal product name | Fluorouracil |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for solution for injection, Solvent for solution for infusion |
| Routes of administration | Intravenous bolus use , Intravenous drip use |

Dosage and administration details:

400 mg/m² BSA as bolus injection, followed by 2400 mg/m² BSA as continuous infusion over about 48 hours on D1/D2 of a 14-day cycle.

| | |
|--|--|
| Investigational medicinal product name | Folinic acid |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for injection/infusion, Solution for infusion |
| Routes of administration | Intravenous drip use |

Dosage and administration details:

400 mg/m² BSA as intravenous infusion over about 2 hours on D1 of a 14-day cycle.

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

Dosage and administration details:

180 mg/m² BSA as intravenous infusion over about 90 minutes on D1 of a 14-day cycle.

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

Dosage and administration details:

85 mg/m² BSA as intravenous infusion over about 2 hours on D1 of a 14-day cycle.

| Number of subjects in period 2 | Arm A (rash-positive) | Arm B (rash-negative) |
|---------------------------------------|-----------------------|-----------------------|
| Started | 89 | 27 |
| Completed | 89 | 27 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|----------------------------------|
| Reporting group title | Run-in with Gemcitabin/Erlotinib |
|-----------------------|----------------------------------|

Reporting group description:

All patients of the Full-Analysis Population, who were administered at least one dose of gemcitabine or erlotinib during the Run-in period (first four weeks of treatment)

| Reporting group values | Run-in with Gemcitabin/Erlotinib | Total | |
|--|----------------------------------|-------|--|
| Number of subjects | 144 | 144 | |
| Age categorical Units: Subjects | | | |
| In utero | | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | | 0 | |
| Newborns (0-27 days) | | 0 | |
| Infants and toddlers (28 days-23 months) | | 0 | |
| Children (2-11 years) | | 0 | |
| Adolescents (12-17 years) | | 0 | |
| Adults (18-64 years) | | 0 | |
| From 65-84 years | | 0 | |
| 85 years and over | | 0 | |
| Age continuous Units: years | | | |
| median | 63.5 | | |
| full range (min-max) | 24.0 to 75.0 | - | |
| Gender categorical Units: Subjects | | | |
| Female | 57 | 57 | |
| Male | 87 | 87 | |
| ECOG Performance Status Units: Subjects | | | |
| ECOG PS 0 | 87 | 87 | |
| ECOG PS 1 | 57 | 57 | |

Subject analysis sets

| | |
|----------------------------|----------------------------------|
| Subject analysis set title | Rash-positive (primary endpoint) |
|----------------------------|----------------------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

All patients, who are rash-positive after 4 weeks treatment with gemcitabine and erlotinib (all except one patient continued treatment with gemcitabine and erlotinib after the Run-in phase)

| | |
|----------------------------|--------------------------------|
| Subject analysis set title | Patients - efficacy assessable |
|----------------------------|--------------------------------|

| | |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

Patients of Full Analysis Set with: (a) at least two cycles for patients in arm A (i.e. cycle 1A+1B=2x28=56 days) and at least until cycle 2 for patients in arm B (i.e. cycle 1A+1+2=28+14+14=56days, (b) one restaging acc. to RECIST 1.1 during study treatment. Unless (a) and (b) are unsatisfied due to early progression/death

| | |
|----------------------------|----------------------|
| Subject analysis set title | All patients treated |
| Subject analysis set type | Full analysis |

Subject analysis set description:

All patients who have been treated with at least one dose of study medication (gemcitabine, erlotinib, FOLFIRINOX). One further patient was excluded from the Full Analysis due to later detected violation of inclusion- and exclusion criteria.

| Reporting group values | Rash-positive (primary endpoint) | Patients - efficacy assessable | All patients treated |
|---|-------------------------------------|-----------------------------------|----------------------|
| Number of subjects | 90 | 123 | 144 |
| Age categorical Units: Subjects | | | |
| In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over | | | |
| Age continuous Units: years | | | |
| median | 63.0 | 63.0 | 63.5 |
| full range (min-max) | 24.0 to 75.0 | 24.0 to 75.0 | 24.0 to 75.0 |
| Gender categorical Units: Subjects | | | |
| Female | 32 | 47 | 57 |
| Male | 58 | 76 | 87 |
| ECOG Performance Status Units: Subjects | | | |
| ECOG PS 0 | 64 | 78 | 87 |
| ECOG PS 1 | 26 | 45 | 57 |

End points

End points reporting groups

| | |
|-----------------------|--------|
| Reporting group title | Run-in |
|-----------------------|--------|

Reporting group description:

Treatment with gemcitabine 1000 mg/² BSA weekly and erlotinib, 100 mg once daily for 4 weeks. Treatment was discontinued earlier in case of progression of the metastatic pancreatic adenocarcinoma, unacceptable toxicity or other reasons (patient's wish, investigator's decision).

| | |
|-----------------------|-----------------------|
| Reporting group title | Arm A (rash-positive) |
|-----------------------|-----------------------|

Reporting group description:

Patient who had developed skin rash after 4 weeks of treatment with gemcitabine 1000 mg/² BSA weekly and erlotinib 100 mg p.o. once daily in the Run-in phase (first 4 treatment weeks), continued treatment with gemcitabine 1000 mg/² weekly on D1, D7, D14 of each 28-day treatment cycle and erlotinib 100 mg p.o. once daily.

Treatment was continued until progression of the metastatic pancreatic adenocarcinoma, unacceptable toxicity or other reasons (patient's wish, investigator's decision).

| | |
|-----------------------|-----------------------|
| Reporting group title | Arm B (rash-negative) |
|-----------------------|-----------------------|

Reporting group description:

Patient who had developed no skin rash after 4 weeks of treatment with gemcitabine 1000 mg/² BSA weekly and erlotinib 100 mg p.o. once daily in the Run-in phase (first 4 treatment weeks), received further treatment with FOLFIRINOX (fluorouracil, folinic acid, irinotecan, oxaliplatin). Treatment was continued until progression of the metastatic pancreatic adenocarcinoma, unacceptable toxicity or other reasons (patient's wish, investigator's decision). Only rash-negative patients who were given FOLFIRINOX treatment after Run-in are included.

| | |
|----------------------------|----------------------------------|
| Subject analysis set title | Rash-positive (primary endpoint) |
|----------------------------|----------------------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

All patients, who are rash-positive after 4 weeks treatment with gemcitabine and erlotinib (all except one patient continued treatment with gemcitabine and erlotinib after the Run-in phase)

| | |
|----------------------------|--------------------------------|
| Subject analysis set title | Patients - efficacy assessable |
|----------------------------|--------------------------------|

| | |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

Patients of Full Analysis Set with: (a) at least two cycles for patients in arm A (i.e. cycle 1A+1B=2x28=56 days) and at least until cycle 2 for patients in arm B (i.e. cycle 1A+1+2=28+14+14=56days), (b) one restaging acc. to RECIST 1.1 during study treatment. Unless (a) and (b) are unsatisfied due to early progression/death

| | |
|----------------------------|----------------------|
| Subject analysis set title | All patients treated |
|----------------------------|----------------------|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

All patients who have been treated with at least one dose of study medication (gemcitabine, erlotinib, FOLFIRINOX). One further patient was excluded from the Full Analysis due to later detected violation of inclusion- and exclusion criteria.

Primary: 1-year survival rate in patients with skin rash

| | |
|-----------------|--|
| End point title | 1-year survival rate in patients with skin rash ^[1] |
|-----------------|--|

End point description:

The primary endpoint is the 1-year survival rate for patients treated with gemcitabine + erlotinib developing skin rash of any grade during a four-week Run-in phase. Overall survival is calculated from the date of first administration of gemcitabine/erlotinib until date of death, censoring patients still alive with the date of last known contact (confirmatory analysis).

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

End point timeframe:

Survival status of each participating patient is recorded for at least 18 months after the date of enrollment.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The alternative hypothesis of a one-year-survival-rate of 40% was to be differed from the null hypothesis of 25% within a two-sided test (significance level 0.05, power 83%; pre-specified analysis). The alternative hypothesis and the null hypothesis are based on the published historical data in patients treated with gemcitabine/erlotinib in the PA.3 study (Moore 2007) and in patients treated with FOLFIRINOX (Conroy 2011), thus the statistical hypothetical test compared with historical groups.

| End point values | Rash-positive (primary endpoint) | | | |
|---------------------------------|----------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 90 | | | |
| Units: number of patients alive | | | | |
| 40.0% (29.8-50.9%) | 36 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate (ORR)

| | |
|---|-------------------------------|
| End point title | Objective response rate (ORR) |
| End point description: | |
| Percentage of patients who experienced "Complete response" or "Partial response" according to RECIST 1.1 (exploratory analysis) | |
| End point type | Secondary |
| End point timeframe: | |
| Evaluated every 8 weeks from the start of treatment until the end of treatment visit. | |

| End point values | Arm B (rash-negative) | Rash-positive (primary endpoint) | Patients - efficacy assessable | All patients treated |
|------------------------------------|-----------------------|----------------------------------|--------------------------------|----------------------|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 27 | 90 | 123 | 144 |
| Units: number of subjects with ORR | | | | |
| 33.3% (16.5 to 54.0%) | 9 | 0 | 0 | 0 |
| 23.3% (15.1 to 33.4%) | 0 | 21 | 0 | 0 |
| 24.4% | 0 | 0 | 30 | 0 |
| 20.8% | 0 | 0 | 0 | 30 |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

| | |
|-----------------|---------------------------|
| End point title | Progression-free survival |
|-----------------|---------------------------|

End point description:

Progression-free survival is the time from the date of first administration of gemcitabin/erlotinib in Run-in until occurrence of progression or death of any cause. Patients without event will be censored with the last date known to be progression-free (exploratory analysis)

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

End point timeframe:

Progression is evaluated every 8 weeks from the start of treatment until the end of treatment visit by means of imaging procedures. Survival status of each participating patient is recorded for at least 18 months after the date of enrollment.

| End point values | Arm B (rash-negative) | Rash-positive (primary endpoint) | Patients - efficacy assessable | All patients treated |
|---|-----------------------|----------------------------------|--------------------------------|----------------------|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 27 | 90 | 123 | 144 |
| Units: Months | | | | |
| arithmetic mean (confidence interval 95%) | 6.6 (2.6 to 9.6) | 3.8 (3.5 to 4.9) | 3.6 (2.8 to 5.0) | 3.6 (3.2 to 4.7) |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

| | |
|-----------------|------------------|
| End point title | Overall survival |
|-----------------|------------------|

End point description:

Overall survival is calculated from the date of first application of gemcitabine/erlotinib until date of death, censoring patients still alive with the date of last known contact (exploratory analysis).

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

End point timeframe:

Survival status of each participating patient is recorded for at least 18 months after the date of enrollment.

| End point values | Arm B (rash-negative) | Rash-positive (primary endpoint) | Patients - efficacy assessable | All patients treated |
|----------------------------------|-----------------------|----------------------------------|--------------------------------|----------------------|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 27 | 90 | 123 | 144 |
| Units: months | | | | |
| median (confidence interval 95%) | 10.9 (6.6 to 14.0) | 10.1 (9.0 to 12.5) | 10.0 (9.0 to 12.1) | 9.7 (8.0 to 10.9) |

Statistical analyses

No statistical analyses for this end point

Secondary: Disease-control rate (DCR)

| | |
|-----------------|----------------------------|
| End point title | Disease-control rate (DCR) |
|-----------------|----------------------------|

End point description:

Percentage of patients who experienced "Complete response" or "Partial response" or "Stable disease" according to RECIST 1.1 (exploratory analysis)

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

End point timeframe:

Evaluated every 8 weeks from the start of treatment until the end of treatment visit.

| End point values | Arm B (rash-negative) | Rash-positive (primary endpoint) | Patients - efficacy assessable | All patients treated |
|------------------------------------|-----------------------|----------------------------------|--------------------------------|----------------------|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 27 | 90 | 123 | 144 |
| Units: Number of patients with DCR | | | | |
| 63.0% | 17 | 0 | 0 | 0 |
| 66.7% | 0 | 60 | 0 | 0 |
| 61,0% | 0 | 0 | 75 | 0 |
| 54,2% | 0 | 0 | 0 | 78 |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Date of signing informed consent until 28 days after last administration of study medication.

Adverse event reporting additional description:

Patients who received at least one administration of gemcitabine or erlotinib were analyzed as Safety Population. Only treatment-emergent events were analyzed.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 15.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Continued treatment with gemcitabin/erlotinib after Run-in |
|-----------------------|--|

Reporting group description:

Rash-positive patients: Continued treatment with gemcitabine 100 mg/m² BSA weekly i.v. in Week 1-3 of each 28-day cycle and erlotinib 100 mg p.o. once daily after the Run-in phase until progression or unacceptable toxicity.

Only adverse events, experienced after Run-in during continued treatment with gemcitabine and erlotinib are taken into account.

| | |
|-----------------------|-------------------------|
| Reporting group title | FOLFIRINOX after Run-in |
|-----------------------|-------------------------|

Reporting group description:

Treatment with FOLFIRINOX after the Run-in phase:

Oxaliplatin 85 mg/m² on Day 1 of each 14-day cycle; i.v.

Folinic acid 400 mg/m² on Day 1 of each 14-day cycle; i.v.

Irinotecane 180 mg/m² on Day 1 of each 14-day cycle; i.v.

5-fluorouracil 400 mg/m² as bolus, followed by 2400 mg/m² as i.v. infusion over 46 hours

Treatment until progression or unacceptable toxicity.

Only adverse events, experienced after Run-in while receiving FOLFIRINOX treatment, are taken into account.

| | |
|-----------------------|-----------------------------------|
| Reporting group title | Gemcitabine and erlotinib overall |
|-----------------------|-----------------------------------|

Reporting group description:

Patients who were administered at least one dose of gemcitabine or erlotinib in the Run-in phase (first 4 treatment weeks; gemcitabine 1000 mg/m² BSA weekly and erlotinib 100 mg p.o. once daily)

and/or continued application of gemcitabine and erlotinib (gemcitabine 1000 mg/m² BSA on D1, D7, D14 of a 28-day cycle and erlotinib 100 mg p.o. once daily until progression or unacceptable toxicity).

Only adverse event in these treatment periods with treatment with gemcitabin and erlotinib are taken into account. Those adverse events, experienced after Run-in while receiving FOLFIRINOX treatment, are not taken into account.

| Serious adverse events | Continued treatment with gemcitabin/erlotinib after Run-in | FOLFIRINOX after Run-in | Gemcitabine and erlotinib overall |
|---|--|-------------------------|-----------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 42 / 89 (47.19%) | 15 / 28 (53.57%) | 70 / 145 (48.28%) |
| number of deaths (all causes) | 9 | 2 | 16 |
| number of deaths resulting from adverse events | 0 | 1 | 9 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour associated fever | | | |

| | | | |
|--|---|----------------|-----------------|
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 28 (0.00%) | 1 / 145 (0.69%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Circulatory collapse | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 0 / 28 (0.00%) | 1 / 145 (0.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Embolism | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 0 / 28 (0.00%) | 1 / 145 (0.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertension | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 28 (0.00%) | 1 / 145 (0.69%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombosis | Additional description: The pre-printed term was "Thromboembolic events". Thus, the terms thrombosis, pulmonary embolism and jugular vein thrombosis are summarized under "Thrombosis". | | |
| subjects affected / exposed | 5 / 89 (5.62%) | 1 / 28 (3.57%) | 6 / 145 (4.14%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 1 | 0 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Medical device implantation | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 28 (0.00%) | 1 / 145 (0.69%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Catheter site haematoma | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 28 (0.00%) | 1 / 145 (0.69%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chills | | | |

| | | | |
|---|---|----------------|-----------------|
| subjects affected / exposed | 2 / 89 (2.25%) | 0 / 28 (0.00%) | 2 / 145 (1.38%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device dislocation | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 0 / 28 (0.00%) | 1 / 145 (0.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device occlusion | | | |
| subjects affected / exposed | 2 / 89 (2.25%) | 0 / 28 (0.00%) | 2 / 145 (1.38%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 5 / 89 (5.62%) | 2 / 28 (7.14%) | 6 / 145 (4.14%) |
| occurrences causally related to treatment / all | 1 / 6 | 1 / 2 | 2 / 7 |
| deaths causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 1 |
| Impaired healing | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 28 (0.00%) | 1 / 145 (0.69%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 28 (0.00%) | 2 / 145 (1.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain | Additional description: Summarized pre-printed term "Pain" comprising summarized terms "Abdominal pain, back pain, chest pain, abdominal pain upper". | | |
| subjects affected / exposed | 5 / 89 (5.62%) | 2 / 28 (7.14%) | 9 / 145 (6.21%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 2 | 0 / 10 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 89 (3.37%) | 1 / 28 (3.57%) | 5 / 145 (3.45%) |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 1 | 2 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|---|----------------|-----------------|
| Pneumonitis | Additional description: Summarized terms "Pneumonitis" and "Interstitial lung disease". | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 28 (0.00%) | 1 / 145 (0.69%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 1 / 28 (3.57%) | 1 / 145 (0.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 0 / 28 (0.00%) | 1 / 145 (0.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood uric acid increased | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 28 (0.00%) | 1 / 145 (0.69%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 2 / 89 (2.25%) | 0 / 28 (0.00%) | 2 / 145 (1.38%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 28 (0.00%) | 1 / 145 (0.69%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 2 / 89 (2.25%) | 0 / 28 (0.00%) | 5 / 145 (3.45%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood bilirubin increased | Additional description: Terms "Blood bilirubin increased" and "jaundice" | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 28 (0.00%) | 5 / 145 (3.45%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|--|---|----------------|-----------------|
| Weight decreased subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | Additional description: Terms "Cachexia" and "Weight decreased" | | |
| | 0 / 89 (0.00%) | 1 / 28 (3.57%) | 0 / 145 (0.00%) |
| | 0 / 0 | 0 / 1 | 0 / 0 |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Anastomotic complication | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 0 / 28 (0.00%) | 1 / 145 (0.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal fracture | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 1 / 28 (3.57%) | 0 / 145 (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 |
| Cardiac disorders | | | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 28 (0.00%) | 1 / 145 (0.69%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| Additional description: Summarized terms "Cerebrovascular accident" and "Cerebral infarction" | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 1 / 28 (3.57%) | 2 / 145 (1.38%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 0 / 28 (0.00%) | 1 / 145 (0.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 1 / 28 (3.57%) | 2 / 145 (1.38%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anaemia | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 89 (1.12%) | 1 / 28 (3.57%) | 1 / 145 (0.69%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukocytosis | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 28 (0.00%) | 1 / 145 (0.69%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Optic ischaemic neuropathy | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 28 (0.00%) | 1 / 145 (0.69%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 1 / 28 (3.57%) | 1 / 145 (0.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 28 (0.00%) | 1 / 145 (0.69%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 1 / 28 (3.57%) | 1 / 145 (0.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Ileus | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 28 (0.00%) | 2 / 145 (1.38%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subileus | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 28 (0.00%) | 1 / 145 (0.69%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Nausea | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 2 / 89 (2.25%) | 2 / 28 (7.14%) | 4 / 145 (2.76%) |
| occurrences causally related to treatment / all | 1 / 3 | 2 / 2 | 1 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 3 / 89 (3.37%) | 2 / 28 (7.14%) | 5 / 145 (3.45%) |
| occurrences causally related to treatment / all | 1 / 4 | 2 / 2 | 1 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 28 (0.00%) | 1 / 145 (0.69%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 28 (0.00%) | 1 / 145 (0.69%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 0 / 28 (0.00%) | 1 / 145 (0.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Duodenitis | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 1 / 28 (3.57%) | 0 / 145 (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 |
| Hepatobiliary disorders | | | |
| Acute hepatic failure | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 28 (0.00%) | 1 / 145 (0.69%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Bile duct stenosis | | | |
| subjects affected / exposed | 3 / 89 (3.37%) | 0 / 28 (0.00%) | 3 / 145 (2.07%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis | | | |

| | | | |
|---|--|-----------------|-------------------|
| subjects affected / exposed | 0 / 89 (0.00%) | 0 / 28 (0.00%) | 1 / 145 (0.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholestasis | | | |
| subjects affected / exposed | 2 / 89 (2.25%) | 0 / 28 (0.00%) | 5 / 145 (3.45%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic failure | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 0 / 28 (0.00%) | 1 / 145 (0.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Perforation bile duct | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 0 / 28 (0.00%) | 1 / 145 (0.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 28 (0.00%) | 1 / 145 (0.69%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Infections and infestations | | | |
| Abdominal abscess | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 28 (0.00%) | 1 / 145 (0.69%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 28 (0.00%) | 1 / 145 (0.69%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection | Additional description: The pre-printed term was infection without further differentiation. The term infection comprises among others also the terms "Cholangitis", "Peritonitis bacterial", "Atypical pneumonia". | | |
| subjects affected / exposed | 16 / 89 (17.98%) | 3 / 28 (10.71%) | 22 / 145 (15.17%) |
| occurrences causally related to treatment / all | 1 / 16 | 1 / 4 | 2 / 22 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |

| | | | |
|---|----------------|----------------|-----------------|
| Sepsis | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 28 (0.00%) | 1 / 145 (0.69%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 2 / 28 (7.14%) | 0 / 145 (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 |

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

| Non-serious adverse events | Continued treatment with gemcitabin/erlotinib after Run-in | FOLFIRINOX after Run-in | Gemcitabine and erlotinib overall |
|---|--|-------------------------|-----------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 89 / 89 (100.00%) | 28 / 28 (100.00%) | 145 / 145 (100.00%) |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 26 / 89 (29.21%) | 13 / 28 (46.43%) | 37 / 145 (25.52%) |
| occurrences (all) | 30 | 18 | 45 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 31 / 89 (34.83%) | 4 / 28 (14.29%) | 51 / 145 (35.17%) |
| occurrences (all) | 33 | 4 | 54 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 26 / 89 (29.21%) | 9 / 28 (32.14%) | 38 / 145 (26.21%) |
| occurrences (all) | 28 | 11 | 40 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 12 / 89 (13.48%) | 2 / 28 (7.14%) | 15 / 145 (10.34%) |
| occurrences (all) | 15 | 2 | 18 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 18 / 89 (20.22%) | 6 / 28 (21.43%) | 25 / 145 (17.24%) |
| occurrences (all) | 22 | 8 | 30 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 21 / 89 (23.60%) | 4 / 28 (14.29%) | 28 / 145 (19.31%) |
| occurrences (all) | 26 | 16 | 33 |

| | | | |
|--------------------------------------|--|------------------|--------------------|
| Gamma-glutamyltransferase increased | Additional description: Terms "Gamma-glutamyltransferase" and "Gamma-glutamyltransferase increased" | | |
| subjects affected / exposed | 52 / 89 (58.43%) | 21 / 28 (75.00%) | 79 / 145 (54.48%) |
| occurrences (all) | 60 | 27 | 89 |
| Protein total decreased | | | |
| subjects affected / exposed | 7 / 89 (7.87%) | 5 / 28 (17.86%) | 10 / 145 (6.90%) |
| occurrences (all) | 7 | 6 | 12 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 21 / 89 (23.60%) | 4 / 28 (14.29%) | 30 / 145 (20.69%) |
| occurrences (all) | 21 | 6 | 32 |
| Hepatic enzyme increased | Additional description: Summarized pre-printed term "Liver values increased (ALT)" and term "Hepatic enzyme increased" and term "Transaminases" and term "Alanine aminotransferase increased". | | |
| subjects affected / exposed | 79 / 89 (88.76%) | 20 / 28 (71.43%) | 117 / 145 (80.69%) |
| occurrences (all) | 98 | 27 | 140 |
| Blood urea increased | | | |
| subjects affected / exposed | 5 / 89 (5.62%) | 1 / 28 (3.57%) | 5 / 145 (3.45%) |
| occurrences (all) | 6 | 4 | 6 |
| Vascular disorders | | | |
| Hypertension | Additional description: Summarized terms "Hypertension" and "Blood pressure increased". | | |
| subjects affected / exposed | 8 / 89 (8.99%) | 3 / 28 (10.71%) | 11 / 145 (7.59%) |
| occurrences (all) | 9 | 3 | 13 |
| Thrombosis | Additional description: The pre-printed term was "Thromboembolic events". Thus, the terms thrombosis, pulmonary embolism and jugular vein thrombosis are summarized under "Thrombosis". | | |
| subjects affected / exposed | 8 / 89 (8.99%) | 4 / 28 (14.29%) | 11 / 145 (7.59%) |
| occurrences (all) | 10 | 4 | 13 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 10 / 89 (11.24%) | 4 / 28 (14.29%) | 15 / 145 (10.34%) |
| occurrences (all) | 11 | 4 | 16 |
| Dysgeusia | | | |
| subjects affected / exposed | 7 / 89 (7.87%) | 3 / 28 (10.71%) | 13 / 145 (8.97%) |
| occurrences (all) | 8 | 5 | 14 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 13 / 89 (14.61%) | 16 / 28 (57.14%) | 18 / 145 (12.41%) |
| occurrences (all) | 13 | 35 | 18 |
| Blood and lymphatic system disorders | | | |

| | | | |
|--|---|------------------|--------------------|
| Anaemia | | | |
| subjects affected / exposed | 87 / 89 (97.75%) | 25 / 28 (89.29%) | 135 / 145 (93.10%) |
| occurrences (all) | 90 | 33 | 143 |
| Leukopenia | | | |
| subjects affected / exposed | 63 / 89 (70.79%) | 10 / 28 (35.71%) | 98 / 145 (67.59%) |
| occurrences (all) | 88 | 22 | 130 |
| Neutropenia | | | |
| subjects affected / exposed | 26 / 89 (29.21%) | 7 / 28 (25.00%) | 38 / 145 (26.21%) |
| occurrences (all) | 31 | 18 | 46 |
| Lymphopenia | Additional description: Summarized terms "Lymphopenia" and "Lymphocyte count decreased". | | |
| subjects affected / exposed | 9 / 89 (10.11%) | 4 / 28 (14.29%) | 13 / 145 (8.97%) |
| occurrences (all) | 11 | 4 | 15 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 51 / 89 (57.30%) | 14 / 28 (50.00%) | 96 / 145 (66.21%) |
| occurrences (all) | 65 | 22 | 125 |
| Thrombocytosis | | | |
| subjects affected / exposed | 6 / 89 (6.74%) | 5 / 28 (17.86%) | 8 / 145 (5.52%) |
| occurrences (all) | 6 | 6 | 8 |
| General disorders and administration site conditions | | | |
| Chills | | | |
| subjects affected / exposed | 6 / 89 (6.74%) | 0 / 28 (0.00%) | 9 / 145 (6.21%) |
| occurrences (all) | 6 | 0 | 9 |
| Fatigue | | | |
| subjects affected / exposed | 48 / 89 (53.93%) | 19 / 28 (67.86%) | 89 / 145 (61.38%) |
| occurrences (all) | 55 | 43 | 97 |
| Feeling cold | | | |
| subjects affected / exposed | 3 / 89 (3.37%) | 2 / 28 (7.14%) | 3 / 145 (2.07%) |
| occurrences (all) | 4 | 2 | 4 |
| General physical health deterioration | | | |
| subjects affected / exposed | 4 / 89 (4.49%) | 3 / 28 (10.71%) | 10 / 145 (6.90%) |
| occurrences (all) | 5 | 3 | 11 |
| Oedema peripheral | Additional description: Terms "Oedema peripheral" and "Oedema lower leg" | | |
| subjects affected / exposed | 26 / 89 (29.21%) | 8 / 28 (28.57%) | 40 / 145 (27.59%) |
| occurrences (all) | 39 | 10 | 47 |
| Pain | Additional description: Summarized pre-printed term "Pain" comprising summarized terms "Abdominal pain, back pain, chest pain, abdominal pain upper" et others. | | |

| | | | |
|---|---|------------------|--------------------|
| subjects affected / exposed | 54 / 89 (60.67%) | 23 / 28 (82.14%) | 104 / 145 (71.72%) |
| occurrences (all) | 67 | 34 | 123 |
| Pyrexia | | | |
| subjects affected / exposed | 16 / 89 (17.98%) | 3 / 28 (10.71%) | 27 / 145 (18.62%) |
| occurrences (all) | 20 | 3 | 32 |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 23 / 89 (25.84%) | 6 / 28 (21.43%) | 35 / 145 (24.14%) |
| occurrences (all) | 29 | 15 | 42 |
| Diarrhoea | | | |
| subjects affected / exposed | 30 / 89 (33.71%) | 13 / 28 (46.43%) | 59 / 145 (40.69%) |
| occurrences (all) | 35 | 23 | 69 |
| Ascites | | | |
| subjects affected / exposed | 6 / 89 (6.74%) | 1 / 28 (3.57%) | 7 / 145 (4.83%) |
| occurrences (all) | 7 | 1 | 8 |
| Dry mouth | | | |
| subjects affected / exposed | 4 / 89 (4.49%) | 2 / 28 (7.14%) | 8 / 145 (5.52%) |
| occurrences (all) | 4 | 2 | 8 |
| Dyspepsia | | | |
| subjects affected / exposed | 6 / 89 (6.74%) | 2 / 28 (7.14%) | 8 / 145 (5.52%) |
| occurrences (all) | 7 | 3 | 10 |
| Stomatitis | Additional description: The term "Stomatitis" comprises stomatitis and mucositis at another site. | | |
| subjects affected / exposed | 14 / 89 (15.73%) | 8 / 28 (28.57%) | 26 / 145 (17.93%) |
| occurrences (all) | 15 | 19 | 27 |
| Nausea | | | |
| subjects affected / exposed | 49 / 89 (55.06%) | 23 / 28 (82.14%) | 82 / 145 (56.55%) |
| occurrences (all) | 59 | 43 | 96 |
| Vomiting | | | |
| subjects affected / exposed | 21 / 89 (23.60%) | 13 / 28 (46.43%) | 36 / 145 (24.83%) |
| occurrences (all) | 23 | 16 | 43 |
| Flatulence | | | |
| subjects affected / exposed | 5 / 89 (5.62%) | 0 / 28 (0.00%) | 5 / 145 (3.45%) |
| occurrences (all) | 5 | 0 | 5 |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|--|------------------------|------------------------|-------------------------|
| Cough subjects affected / exposed occurrences (all) | 6 / 89 (6.74%) 6 | 2 / 28 (7.14%) 2 | 6 / 145 (4.14%) 6 |
| Dyspnoea subjects affected / exposed occurrences (all) | 14 / 89 (15.73%) 17 | 5 / 28 (17.86%) 5 | 17 / 145 (11.72%) 20 |
| Epistaxis subjects affected / exposed occurrences (all) | 5 / 89 (5.62%) 5 | 0 / 28 (0.00%) 0 | 7 / 145 (4.83%) 9 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia subjects affected / exposed occurrences (all) | 22 / 89 (24.72%) 23 | 10 / 28 (35.71%) 20 | 25 / 145 (17.24%) 27 |
| Dry skin subjects affected / exposed occurrences (all) | 13 / 89 (14.61%) 16 | 5 / 28 (17.86%) 10 | 19 / 145 (13.10%) 23 |
| Night sweats subjects affected / exposed occurrences (all) | 4 / 89 (4.49%) 4 | 1 / 28 (3.57%) 1 | 8 / 145 (5.52%) 8 |
| Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all) | 5 / 89 (5.62%) 6 | 4 / 28 (14.29%) 7 | 6 / 145 (4.14%) 7 |
| Pruritus subjects affected / exposed occurrences (all) | 10 / 89 (11.24%) 11 | 2 / 28 (7.14%) 2 | 21 / 145 (14.48%) 22 |
| Rash subjects affected / exposed occurrences (all) | 15 / 89 (16.85%) 19 | 3 / 28 (10.71%) 3 | 17 / 145 (11.72%) 23 |
| Psychiatric disorders | | | |
| Depression subjects affected / exposed occurrences (all) | 2 / 89 (2.25%) 2 | 2 / 28 (7.14%) 3 | 2 / 145 (1.38%) 2 |
| Musculoskeletal and connective tissue disorders | | | |
| Muscle spasms subjects affected / exposed occurrences (all) | 6 / 89 (6.74%) 8 | 0 / 28 (0.00%) 0 | 6 / 145 (4.14%) 8 |

| | | | |
|------------------------------------|--|-----------------|-------------------|
| Infections and infestations | | | |
| Infection | Additional description: The pre-printed term was infection without further differentiation. The term "Infection" comprises among others also the terms "Cholangitis", "Peritonitis bacterial", "Atypical pneumonia". | | |
| subjects affected / exposed | 21 / 89 (23.60%) | 3 / 28 (10.71%) | 35 / 145 (24.14%) |
| occurrences (all) | 24 | 3 | 38 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 31 / 89 (34.83%) | 6 / 28 (21.43%) | 47 / 145 (32.41%) |
| occurrences (all) | 38 | 11 | 56 |
| Hypokalaemia | Additional description: Summarized terms "Hypokalaemia" and "Blood potassium decreased". | | |
| subjects affected / exposed | 5 / 89 (5.62%) | 6 / 28 (21.43%) | 12 / 145 (8.28%) |
| occurrences (all) | 6 | 12 | 14 |
| Hyperglycaemia | Additional description: Summarized terms "Hyperglycaemia" and "Blood glucose increased". | | |
| subjects affected / exposed | 2 / 89 (2.25%) | 3 / 28 (10.71%) | 5 / 145 (3.45%) |
| occurrences (all) | 2 | 4 | 5 |
| Hyponatraemia | Additional description: Summarized terms "Hyponatraemia" and "Blood sodium decreased". | | |
| subjects affected / exposed | 7 / 89 (7.87%) | 6 / 28 (21.43%) | 9 / 145 (6.21%) |
| occurrences (all) | 8 | 6 | 9 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 2 / 89 (2.25%) | 2 / 28 (7.14%) | 3 / 145 (2.07%) |
| occurrences (all) | 3 | 3 | 4 |
| Hypoalbuminaemia | Additional description: Summarized terms "Hypoalbuminaemia" and "Blood albumin decreased". | | |
| subjects affected / exposed | 12 / 89 (13.48%) | 3 / 28 (10.71%) | 14 / 145 (9.66%) |
| occurrences (all) | 13 | 7 | 16 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported