



Clinical trial results:

ADJUVANT TREATMENT OF FULLY RESECTED STAGE III COLON CANCER WITH FOLFOX-4 VERSUS FOLFOX-4 PLUS CETUXIMAB

Tratamiento adyuvante con FOLFOX-4 versus FOLFOX-4 + cetuximab para el cáncer de colon en estadio III extirpado completamente

Summary

| | |
|--------------------------|-------------------------|
| EudraCT number | 2005-003463-23 |
| Trial protocol | ES GB DE AT BE PT DK IT |
| Global end of trial date | 15 October 2016 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 29 March 2022 |
| First version publication date | 29 March 2022 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | PETACC 8 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00265811 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Fédération Francophone de Cancérologie Digestive (FFCD) |
| Sponsor organisation address | 7 Bd Jeanne d'Arc, Dijon, France, |
| Public contact | Karine Le Malicot, Fédération Francophone de Cancérologie Digestive (FFCD), karine.le-malicot@u-bourgogne.fr |
| Scientific contact | Karine Le Malicot, Fédération Francophone de Cancérologie Digestive (FFCD), karine.le-malicot@u-bourgogne.fr |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 31 August 2012 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 30 June 2011 |
| Global end of trial reached? | Yes |
| Global end of trial date | 15 October 2016 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to assess and to compare the disease free survival curves according to treatment arm in completely resected stage III colon cancer.

Protection of trial subjects:

The study was done in accordance with the Declaration of Helsinki (amended 2000) and the International Conference on Harmonization of Technical Requirements of Pharmaceuticals for Human Use (ICH) Note for Guidance on Good Clinical Practice and approved by the appropriate Ethics Committees.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 22 December 2005 |
| 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 | Portugal: 72 |
| Country: Number of subjects enrolled | Spain: 666 |
| Country: Number of subjects enrolled | United Kingdom: 70 |
| Country: Number of subjects enrolled | Austria: 127 |
| Country: Number of subjects enrolled | Belgium: 205 |
| Country: Number of subjects enrolled | Denmark: 28 |
| Country: Number of subjects enrolled | France: 794 |
| Country: Number of subjects enrolled | Germany: 278 |
| Country: Number of subjects enrolled | Italy: 319 |
| Worldwide total number of subjects | 2559 |
| EEA total number of subjects | 2489 |

Notes:

Subjects enrolled per age group

| | |
|--|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 | 0 |

| | |
|--|------|
| wk | |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 1711 |
| From 65 to 84 years | 848 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Between Dec 22, 2005, and Nov 5, 2009, 2559 patients were enrolled from 340 sites in Europe and randomly assigned to treatment (2096 were randomised before June 17, 2008).

Pre-assignment

Screening details:

After checking the inclusion and non-inclusion criteria, patients were randomized to the protocol. We did this open-label randomised, controlled, multinational phase 3 study in patients aged between 18 and 75 years with pathologically confirmed stage III colon adenocarcinoma.

Period 1

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

Blinding implementation details:

Open-label study

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|------------------------|
| Arm title | FOLFOX4 plus Cetuximab |
|------------------|------------------------|

Arm description:

Patients received FOLFOX4 every 2 weeks (1 cycle): 85 mg/m² oxaliplatin (2 h infusion) on day 1, 200 mg/m² leucovorin on days 1 and 2, followed by 400 mg/m² fluorouracil (bolus), then 600 mg/m² fluorouracil (continuous infusion during 22 h), with weekly cetuximab, which was given on day 1, 400 mg/m² (2 h infusion) the first week, then every week at 250 mg/m² (1 h infusion) for subsequent infusions. Treatment was continued for 12 cycles. Patients discontinued after completion of study treatment, occurrence of an unacceptable toxic effect, any disease recurrence, or withdrawal of consent.

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | FOLFOX4 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

FOLFOX4 every 2 weeks (1 cycle): 85 mg/m² oxaliplatin (2 h infusion) on day 1, 200 mg/m² leucovorin on days 1 and 2, followed by 400 mg/m² fluorouracil (bolus), then 600 mg/m² fluorouracil (continuous infusion during 22 h).

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

Dosage and administration details:

Weekly cetuximab, which was given on day 1, 400 mg/m² (2 h infusion) the first week, then every week at 250 mg/m² (1 h infusion) for subsequent infusions.

| | |
|------------------|---------|
| Arm title | FOLFOX4 |
|------------------|---------|

Arm description:

Patients received FOLFOX4 every 2 weeks (1 cycle): 85 mg/m² oxaliplatin (2 h infusion) on day 1, 200 mg/m² leucovorin on days 1 and 2, followed by 400 mg/m² fluorouracil (bolus), then 600 mg/m² fluorouracil (continuous infusion during 22 h). Treatment was continued for 12 cycles. Patients

discontinued after completion of study treatment, occurrence of an unacceptable toxic effect, any disease recurrence, or withdrawal of consent.

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | FOLFOX4 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

FOLFOX4 every 2 weeks (1 cycle): 85 mg/m² oxaliplatin (2 h infusion) on day 1, 200 mg/m² leucovorin on days 1 and 2, followed by 400 mg/m² fluorouracil (bolus), then 600 mg/m² fluorouracil (continuous infusion during 22 h).

| Number of subjects in period 1^[1] | FOLFOX4 plus Cetuximab | FOLFOX4 |
|---|------------------------|---------|
| Started | 791 | 811 |
| Completed | 785 | 805 |
| Not completed | 6 | 6 |
| Kras mutated tumor | 1 | - |
| Not treated Patients | 5 | 4 |
| Kras Mutated Tumours | - | 2 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The presented results are on the target population meaning the Kras Wild-type treated patients that is why numbers are different from the baseline period. Some patients were in fact Kras mutated patients or some were never treated.

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------------------|
| Reporting group title | FOLFOX4 plus Cetuximab |
|-----------------------|------------------------|

Reporting group description:

Patients received FOLFOX4 every 2 weeks (1 cycle): 85 mg/m² oxaliplatin (2 h infusion) on day 1, 200 mg/m² leucovorin on days 1 and 2, followed by 400 mg/m² fluorouracil (bolus), then 600 mg/m² fluorouracil (continuous infusion during 22 h), with weekly cetuximab, which was given on day 1, 400 mg/m² (2 h infusion) the first week, then every week at 250 mg/m² (1 h infusion) for subsequent infusions. Treatment was continued for 12 cycles. Patients discontinued after completion of study treatment, occurrence of an unacceptable toxic effect, any disease recurrence, or withdrawal of consent.

| | |
|-----------------------|---------|
| Reporting group title | FOLFOX4 |
|-----------------------|---------|

Reporting group description:

Patients received FOLFOX4 every 2 weeks (1 cycle): 85 mg/m² oxaliplatin (2 h infusion) on day 1, 200 mg/m² leucovorin on days 1 and 2, followed by 400 mg/m² fluorouracil (bolus), then 600 mg/m² fluorouracil (continuous infusion during 22 h). Treatment was continued for 12 cycles. Patients discontinued after completion of study treatment, occurrence of an unacceptable toxic effect, any disease recurrence, or withdrawal of consent.

| Reporting group values | FOLFOX4 plus Cetuximab | FOLFOX4 | Total |
|--|------------------------|----------|-------|
| Number of subjects | 791 | 811 | 1602 |
| 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 | | | |
| Age at baseline | | | |
| Units: years | | | |
| median | 60 | 60 | |
| full range (min-max) | 19 to 75 | 21 to 75 | - |
| Gender categorical Units: Subjects | | | |
| Female | 323 | 343 | 666 |
| Male | 468 | 468 | 936 |

Subject analysis sets

| | |
|----------------------------|----------------------------------|
| Subject analysis set title | Kras Exon 2 Wild-type population |
|----------------------------|----------------------------------|

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

Subject analysis set description:

All randomized KRAS wild-type patients with signed (Main and KRAS) Informed Consent Forms will be included in this analysis set, in the treatment arm assigned at randomization, irrespective of the

treatment actually received, and irrespective of the violation of baseline eligibility criteria, other protocol deviations or the availability of post-randomization data.

This population set will be used for the primary analyses of all primary and secondary efficacy variables.

| Reporting group values | Kras Exon 2 Wild-type population | | |
|---|----------------------------------|--|--|
| Number of subjects | 1602 | | |
| 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 | | | |
| Age at baseline | | | |
| Units: years | | | |
| median | 60 | | |
| full range (min-max) | 19 to 75 | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 666 | | |
| Male | 936 | | |

End points

End points reporting groups

| | |
|-----------------------|------------------------|
| Reporting group title | FOLFOX4 plus Cetuximab |
|-----------------------|------------------------|

Reporting group description:

Patients received FOLFOX4 every 2 weeks (1 cycle): 85 mg/m² oxaliplatin (2 h infusion) on day 1, 200 mg/m² leucovorin on days 1 and 2, followed by 400 mg/m² fluorouracil (bolus), then 600 mg/m² fluorouracil (continuous infusion during 22 h), with weekly cetuximab, which was given on day 1, 400 mg/m² (2 h infusion) the first week, then every week at 250 mg/m² (1 h infusion) for subsequent infusions. Treatment was continued for 12 cycles. Patients discontinued after completion of study treatment, occurrence of an unacceptable toxic effect, any disease recurrence, or withdrawal of consent.

| | |
|-----------------------|---------|
| Reporting group title | FOLFOX4 |
|-----------------------|---------|

Reporting group description:

Patients received FOLFOX4 every 2 weeks (1 cycle): 85 mg/m² oxaliplatin (2 h infusion) on day 1, 200 mg/m² leucovorin on days 1 and 2, followed by 400 mg/m² fluorouracil (bolus), then 600 mg/m² fluorouracil (continuous infusion during 22 h). Treatment was continued for 12 cycles. Patients discontinued after completion of study treatment, occurrence of an unacceptable toxic effect, any disease recurrence, or withdrawal of consent.

| | |
|----------------------------|----------------------------------|
| Subject analysis set title | Kras Exon 2 Wild-type population |
|----------------------------|----------------------------------|

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

Subject analysis set description:

All randomized KRAS wild-type patients with signed (Main and KRAS) Informed Consent Forms will be included in this analysis set, in the treatment arm assigned at randomization, irrespective of the treatment actually received, and irrespective of the violation of baseline eligibility criteria, other protocol deviations or the availability of post-randomization data.

This population set will be used for the primary analyses of all primary and secondary efficacy variables.

Primary: Disease-Free Survival (DFS)

| | |
|-----------------|-----------------------------|
| End point title | Disease-Free Survival (DFS) |
|-----------------|-----------------------------|

End point description:

DFS was defined as the interval from randomisation to locoregional or metastatic recurrence, the appearance of a secondary colon or rectal cancer, or death, whichever occurred first.

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

End point timeframe:

until the end of the follow-up or appearance of an event

| End point values | FOLFOX4 plus Cetuximab | FOLFOX4 | | |
|---|------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 791 | 811 | | |
| Units: patients | | | | |
| Patients with locoregional or metastatic recurrence | 190 | 179 | | |
| Patients alive without event | 601 | 632 | | |

Statistical analyses

| | |
|----------------------------|---------------------------------|
| Statistical analysis title | Kaplan-Meier and log -rank test |
|----------------------------|---------------------------------|

Statistical analysis description:

DFS and overall survival with the Kaplan-Meier technique²² (primary analysis) and compared survival with a stratified two-sided log-rank test.

| | |
|---|----------------------------------|
| Comparison groups | FOLFOX4 plus Cetuximab v FOLFOX4 |
| Number of subjects included in analysis | 1602 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.66 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.85 |
| upper limit | 1.29 |

Secondary: Overall Survival

| | |
|---|------------------|
| End point title | Overall Survival |
| End point description: | |
| OS was defined as the interval from randomisation to death, whichever occurred first. | |
| End point type | Secondary |
| End point timeframe: | |
| until the end of the follow-up or appearance of death | |

| End point values | FOLFOX4 plus Cetuximab | FOLFOX4 | | |
|-----------------------------|------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 791 | 811 | | |
| Units: patients | | | | |
| Death | 94 | 85 | | |
| Alive patients | 697 | 726 | | |

Statistical analyses

| | |
|---|----------------------------------|
| Statistical analysis title | Kaplan-Meier and log -rank test |
| Comparison groups | FOLFOX4 plus Cetuximab v FOLFOX4 |
| Number of subjects included in analysis | 1602 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.56 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.09 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.81 |
| upper limit | 1.47 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During treatment period and not earlier than 30 days after the last cycle.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 14.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------------|
| Reporting group title | Folfox + Cetuximab |
|-----------------------|--------------------|

Reporting group description:

all patients with signed (Main and KRAS) Informed Consent Forms who started treatment with available KRAS determination and with a KRAS wild-type status, i.e. without mutations located within the codon 12 and 13 of the KRAS gene and randomized in the Folfox +Ceuximab group

| | |
|-----------------------|--------|
| Reporting group title | Folfox |
|-----------------------|--------|

Reporting group description:

all patients with signed (Main and KRAS) Informed Consent Forms who started treatment with available KRAS determination and with a KRAS wild-type status, i.e. without mutations located within the codon 12 and 13 of the KRAS gene and randomized in the Folfox group

| Serious adverse events | Folfox + Cetuximab | Folfox | |
|---|--------------------|--------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 212 / 785 (27.01%) | 148 / 805 (18.39%) | |
| number of deaths (all causes) | 94 | 85 | |
| number of deaths resulting from adverse events | 5 | 3 | |
| Investigations | | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 10 / 785 (1.27%) | 6 / 805 (0.75%) | |
| occurrences causally related to treatment / all | 10 / 10 | 6 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 785 (0.13%) | 0 / 805 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Nervous system disorders | | | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 1 / 785 (0.13%) | 1 / 805 (0.12%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |

| | | | |
|--|------------------|------------------|--|
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 14 / 785 (1.78%) | 16 / 805 (1.99%) | |
| occurrences causally related to treatment / all | 11 / 14 | 13 / 16 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 0 / 785 (0.00%) | 1 / 805 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Sudden death | | | |
| subjects affected / exposed | 1 / 785 (0.13%) | 0 / 805 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 8 / 785 (1.02%) | 1 / 805 (0.12%) | |
| occurrences causally related to treatment / all | 8 / 8 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 3 / 785 (0.38%) | 0 / 805 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 39 / 785 (4.97%) | 16 / 805 (1.99%) | |
| occurrences causally related to treatment / all | 38 / 39 | 16 / 16 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 14 / 785 (1.78%) | 4 / 805 (0.50%) | |
| occurrences causally related to treatment / all | 13 / 14 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 11 / 785 (1.40%) | 5 / 805 (0.62%) | |
| occurrences causally related to treatment / all | 8 / 11 | 2 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 13 / 785 (1.66%) | 10 / 805 (1.24%) | |
| occurrences causally related to treatment / all | 9 / 13 | 9 / 10 | |
| deaths causally related to treatment / all | 1 / 1 | 1 / 1 | |
| Pulmonary fibrosis | | | |
| subjects affected / exposed | 2 / 785 (0.25%) | 0 / 805 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 785 (0.13%) | 1 / 805 (0.12%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Infections and infestations | | | |
| Device related infection | | | |
| subjects affected / exposed | 8 / 785 (1.02%) | 4 / 805 (0.50%) | |
| occurrences causally related to treatment / all | 1 / 8 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 6 / 785 (0.76%) | 5 / 805 (0.62%) | |
| occurrences causally related to treatment / all | 5 / 6 | 4 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 6 / 785 (0.76%) | 4 / 805 (0.50%) | |
| occurrences causally related to treatment / all | 4 / 6 | 3 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 4 / 785 (0.51%) | 2 / 805 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Folfox + Cetuximab | Folfox | |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 784 / 785 (99.87%) | 804 / 805 (99.88%) | |
| Investigations | | | |
| Neutrophils count decreased | | | |
| subjects affected / exposed | 533 / 785 (67.90%) | 593 / 805 (73.66%) | |
| occurrences (all) | 533 | 593 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 497 / 785 (63.31%) | 599 / 805 (74.41%) | |
| occurrences (all) | 497 | 599 | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 449 / 785 (57.20%) | 481 / 805 (59.75%) | |
| occurrences (all) | 449 | 481 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 202 / 785 (25.73%) | 162 / 805 (20.12%) | |
| occurrences (all) | 202 | 162 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 209 / 785 (26.62%) | 177 / 805 (21.99%) | |
| occurrences (all) | 209 | 177 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 133 / 785 (16.94%) | 137 / 805 (17.02%) | |
| occurrences (all) | 133 | 137 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 115 / 785 (14.65%) | 130 / 805 (16.15%) | |
| occurrences (all) | 115 | 130 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 100 / 785 (12.74%) | 124 / 805 (15.40%) | |
| occurrences (all) | 100 | 124 | |
| Nervous system disorders | | | |

| | | | |
|---|---------------------------|---------------------------|--|
| Neuropathy peripheral subjects affected / exposed occurrences (all) | 651 / 785 (82.93%) 651 | 723 / 805 (89.81%) 723 | |
| Dysgeusia subjects affected / exposed occurrences (all) | 146 / 785 (18.60%) 146 | 157 / 805 (19.50%) 157 | |
| Headache subjects affected / exposed occurrences (all) | 64 / 785 (8.15%) 64 | 89 / 805 (11.06%) 89 | |
| General disorders and administration site conditions | | | |
| Asthenia subjects affected / exposed occurrences (all) | 502 / 785 (63.95%) 502 | 508 / 805 (63.11%) 508 | |
| Mucosal inflammation subjects affected / exposed occurrences (all) | 414 / 785 (52.74%) 414 | 289 / 805 (35.90%) 289 | |
| Blood and lymphatic system disorders | | | |
| Leukopenia subjects affected / exposed occurrences (all) | 117 / 785 (14.90%) 117 | 120 / 805 (14.91%) 120 | |
| Eye disorders | | | |
| Conjunctivitis subjects affected / exposed occurrences (all) | 90 / 785 (11.46%) 90 | 37 / 805 (4.60%) 37 | |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 491 / 785 (62.55%) 491 | 500 / 805 (62.11%) 500 | |
| Nausea subjects affected / exposed occurrences (all) | 447 / 785 (56.94%) 447 | 528 / 805 (65.59%) 528 | |
| Vomiting subjects affected / exposed occurrences (all) | 232 / 785 (29.55%) 232 | 268 / 805 (33.29%) 268 | |
| Constipation | | | |

| | | | |
|---|--------------------|--------------------|--|
| subjects affected / exposed | 240 / 785 (30.57%) | 240 / 805 (29.81%) | |
| occurrences (all) | 240 | 240 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Epistaxis | | | |
| subjects affected / exposed | 121 / 785 (15.41%) | 103 / 805 (12.80%) | |
| occurrences (all) | 121 | 103 | |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 707 / 785 (90.06%) | 25 / 805 (3.11%) | |
| occurrences (all) | 707 | 25 | |
| Palmar-plantar erythrodysesthesia syndrome | | | |
| subjects affected / exposed | 210 / 785 (26.75%) | 85 / 805 (10.56%) | |
| occurrences (all) | 210 | 85 | |
| Dry skin | | | |
| subjects affected / exposed | 177 / 785 (22.55%) | 22 / 805 (2.73%) | |
| occurrences (all) | 177 | 22 | |
| Dermatitis allergic | | | |
| subjects affected / exposed | 102 / 785 (12.99%) | 70 / 805 (8.70%) | |
| occurrences (all) | 102 | 70 | |
| Skin fissures | | | |
| subjects affected / exposed | 148 / 785 (18.85%) | 8 / 805 (0.99%) | |
| occurrences (all) | 148 | 8 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 203 / 785 (25.86%) | 158 / 805 (19.63%) | |
| occurrences (all) | 203 | 158 | |
| Hypokalemia | | | |
| subjects affected / exposed | 80 / 785 (10.19%) | 39 / 805 (4.84%) | |
| occurrences (all) | 80 | 39 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|--|
| 25 June 2007 | <p>Correction of participating countries, provision of details of all involved groups and country coordinating investigators (changed for Austria and Germany)</p> <p>Provision of clear definitions of the conditions to be fulfilled and the expected time points for primary and final analyses, clarification of definition of end of trial</p> <p>Clarification of visit and assessment schedule</p> <p>At the request of the IDMC, introduction of electrolyte measurement at baseline, 3 months, 6 months after start of treatment, at the end of treatment Visit and at the second follow-up visit (12 months after surgery) if still abnormal</p> <p>Clarification of time intervals for colonoscopy</p> <p>Update of pretreatment recommendations before cetuximab administrations: addition of corticosteroid</p> <p>Clarification of dosage reduction and treatment continuation rules</p> <p>Harmonization of description of the adverse events page with the CRF</p> <p>Update of informed consent based on changes introduced by this amendment (main study and for translational research)</p> <p>Update of planned statistical analyses</p> <p>Correction of errors</p> |
| 30 April 2008 | <p>* Addition of a second primary objective, namely the comparison of treatments in patients with KRAS wild type tumors</p> <ul style="list-style-type: none">• Adjustment of the risk reduction (hazard ratio) expected from the addition of cetuximab, in the entire study population.• Implementation of one interim analysis for the entire study population and one for the population of patients with KRAS wild type tumors• Increase of the total sample size from 2000 to 2842 patients to achieve the necessary number of events for the primary statistical analysis within a reasonable time frame, considering the adjustments of the individual alpha required because of two primary endpoints and the implementation of interim analysis and the need to maintain the original power of 90%.• Update of the planned statistical analyses and related assumptions, considering the additional primary objective• Introduction of retrospective KRAS assessment in all patients• Clarification of time interval between curative R0 resection and start of treatment• Update of the Patient Information based on introduction of KRAS assessment (main study)• Update of the handling instructions and compatibility of cetuximab with various infusion set materials |

| | |
|----------------|--|
| 14 August 2008 | <ul style="list-style-type: none"> • Introduction of an inclusion criterion regarding KRAS status. • Introduction of prospective KRAS assessment in all new patients. The specific logistics are described in a separate document. • The only primary objective will be the comparison of disease free survival (DFS) between the two treatment arms in the population of patients with KRAS wild-type tumors. • Addition of a new secondary objective, namely the comparison of DFS in the entire population of all patients randomized up to 24:00h, 17 June 2008 (to be performed only if a significant effect on DFS, in the KRAS wild-type population is seen). • Interim analysis only for the primary objective in patients with a KRAS wild-type tumor. • In total 2099 patients have been included until the recruitment stop on 17 June 2008, of whom an estimated 957 patients have assessable KRAS wild-type tumors. An additional 450 patients with a KRAS wild-type tumor should be included to achieve the necessary number of events for the primary statistical analysis, within a reasonable time frame. Therefore, it is estimated that 825 patients will need to be assessed for the KRAS status of their tumors after the restart of patient enrollment (assuming 57.5% will be KRAS wild-type and there will be 5% withdrawals, for other reasons, prior to randomization). • Prolongation of the survival follow-up to 7 years after randomization of the last patient (i.e. 10.5 years in total assuming a recruitment period of 3.5 years). • Update of the planned statistical analyses and related assumptions, considering the population change for primary analysis. • Update of the Patient Information based on introduction of KRAS assessment (main study) and introduction of a new patient information and informed consent necessary for the prescreening of patients for KRAS status. • Update of Translational Research sections • Corrections of errors |
| 30 June 2009 | <p>Change of an inclusion criterion regarding the age of the patients. The FFCD has decided to follow the additional DSMB recommendations regarding patients aged 71 or older which has strongly recommended taking a precautionary measure, no longer to include patients aged 71 or older (at screening), because of an increased risk of toxicity or death observed in the population > 70 years old in the PETACC8 study as compared to the population < 71 years old, whatever the treatment arm is. Furthermore, these results are in line with the analysis of the ACCENT database presented at the main ASCO meeting (2009) that support the use of 5-FU-based regimens without Oxaliplatin in elderly patients >70 years old (McCleary et al., ASCO 2009).</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/24928083>