# Clinical trial results:
# A Phase II, Multicenter, Open-Label, Randomized Study Evaluating the Efficacy and Safety of FOLFIRI + MEHD7945A versus FOLFIRI + Cetuximab in Second Line in Patients with KRAS Wild-Type Metastatic Colorectal Cancer

## Summary

| | |
|---|---|
| EudraCT number | 2011-005547-27 |
| Trial protocol | DE GB BE ES IT |
| Global end of trial date | 26 November 2014 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 26 March 2016 |
| First version publication date | 26 March 2016 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | GO28074 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01652482 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | F. Hoffmann-La Roche AG |
| Sponsor organisation address | Grenzacherstrasse124, Basel, Switzerland, CH-4070 |
| Public contact | F.Hoffmann-LaRocheAG, Roche Trial Information Hotline, +41 616878333, global.trial_information@roche.com |
| Scientific contact | F.Hoffmann-LaRocheAG, Roche Trial Information Hotline, +41 616878333, global.trial_information@roche.com |

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 | 26 February 2015 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 26 November 2014 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of the trial was to evaluate the efficacy of folinic acid-fluorouracil-Irinotecan (FOLFIRI) + MEHD7945A versus FOLFIRI + cetuximab in participants with KRAS wild-type metastatic colorectal cancer (mCRC) and in participants with KRAS wild - type mCRC whose tumors expressed low levels of Human Epidermal Growth Factor Receptor 3 (HER3).

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP) and investigators were trained according to applicable Sponsor standard operating procedures (SOPs).

| |
|---|
| Background therapy: - |
| Evidence for comparator: - |

| | |
|---|---|
| Actual start date of recruitment | 22 October 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 | Spain: 19 |
| Country: Number of subjects enrolled | United Kingdom: 10 |
| Country: Number of subjects enrolled | Belgium: 5 |
| Country: Number of subjects enrolled | France: 2 |
| Country: Number of subjects enrolled | Germany: 11 |
| Country: Number of subjects enrolled | Italy: 13 |
| Country: Number of subjects enrolled | Australia: 27 |
| Country: Number of subjects enrolled | United States: 22 |
| Country: Number of subjects enrolled | New Zealand: 22 |
| Country: Number of subjects enrolled | Romania: 3 |
| Worldwide total number of subjects | 134 |
| EEA total number of subjects | 63 |

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) | 74 |
| From 65 to 84 years | 59 |
| 85 years and over | 1 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Participant screening was conducted from Day -14 to Day -1.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | FOLFIRI+ MEHD7945A |

Arm description:

Participants received MEHD7945A 1100 milligrams (mg) intravenous (IV) infusion every two weeks (14-day cycle) until unacceptable toxicity, documented disease progression or death. Participants also received 5 fluorouracil (5-FU) 400 milligrams per square meter (mg/m^2) as an IV bolus and then 5-FU 2400 mg/m^2 as a continuous IV infusion, irinotecan 180 milligrams per square meter (mg/m^2) IV infusion concurrently (using a y connector) with leucovorin 400 mg/m^2 (racemic form) or 200 mg/m^2 (L-isomer form) IV infusion (FOLFIRI) on Day 1 of 14-day continuous cycles.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | MEHD7945A |
| Investigational medicinal product code | RO5541078 |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

1100 mg IV infusion every two weeks

| | |
|---|---|
| **Arm title** | FOLFIRI + Cetuximab |

Arm description:

All participants received cetuximab 400 mg/m^2 initial dose followed by 250 mg/m^2 IV infusion once a week until unacceptable toxicity, documented disease progression or death. Participants also received FOLFIRI on Day 1 of 14-day continuous cycles.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Cetuximab |
| Investigational medicinal product code | |
| Other name | Erbitux |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

400 mg/m^2 initial dose followed by 250 mg/m^2 IV infusion once a week

| **Number of subjects in period 1** | FOLFIRI+ MEHD7945A | FOLFIRI + Cetuximab |
|---|---|---|
| Started | 68 | 66 |
| Completed | 0 | 0 |
| Not completed | 68 | 66 |
| Consent withdrawn by subject | 5 | 3 |
| Randomized but not enrolled | - | 1 |
| Death | 34 | 33 |
| Study termination by sponsor | 28 | 29 |
| Lost to follow-up | 1 | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | FOLFIRI+ MEHD7945A |
| Reporting group description: | |
| Participants received MEHD7945A 1100 milligrams (mg) intravenous (IV) infusion every two weeks (14-day cycle) until unacceptable toxicity, documented disease progression or death. Participants also received 5 fluorouracil (5-FU) 400 milligrams per square meter (mg/m^2) as an IV bolus and then 5-FU 2400 mg/m^2 as a continuous IV infusion, irinotecan 180 milligrams per square meter (mg/m^2) IV infusion concurrently (using a y connector) with leucovorin 400 mg/m^2 (racemic form) or 200 mg/m^2 (L-isomer form) IV infusion (FOLFIRI) on Day 1 of 14-day continuous cycles. | |
| Reporting group title | FOLFIRI + Cetuximab |
| Reporting group description: | |
| All participants received cetuximab 400 mg/m^2 initial dose followed by 250 mg/m^2 IV infusion once a week until unacceptable toxicity, documented disease progression or death. Participants also received FOLFIRI on Day 1 of 14-day continuous cycles. | |

| Reporting group values | FOLFIRI+ MEHD7945A | FOLFIRI + Cetuximab | Total |
|---|---|---|---|
| Number of subjects | 68 | 66 | 134 |
| Age categorical<br>Units: Subjects | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 59.9 | 61.8 | |
| standard deviation | ± 12.4 | ± 12.5 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 32 | 19 | 51 |
| Male | 36 | 46 | 82 |
| Not recorded | 0 | 1 | 1 |

## End points

### End points reporting groups

| Reporting group title | FOLFIRI+ MEHD7945A |
|---|---|

Reporting group description:

Participants received MEHD7945A 1100 milligrams (mg) intravenous (IV) infusion every two weeks (14-day cycle) until unacceptable toxicity, documented disease progression or death. Participants also received 5 fluorouracil (5-FU) 400 milligrams per square meter (mg/m^2) as an IV bolus and then 5-FU 2400 mg/m^2 as a continuous IV infusion, irinotecan 180 milligrams per square meter (mg/m^2) IV infusion concurrently (using a y connector) with leucovorin 400 mg/m^2 (racemic form) or 200 mg/m^2 (L-isomer form) IV infusion (FOLFIRI) on Day 1 of 14-day continuous cycles.

| Reporting group title | FOLFIRI + Cetuximab |
|---|---|

Reporting group description:

All participants received cetuximab 400 mg/m^2 initial dose followed by 250 mg/m^2 IV infusion once a week until unacceptable toxicity, documented disease progression or death. Participants also received FOLFIRI on Day 1 of 14-day continuous cycles.

### Primary: Percentage of Participants With Disease Progression or Death

| End point title | Percentage of Participants With Disease Progression or Death[1] |
|---|---|

End point description:

Tumor assessments were performed according to modified Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1). Progressive Disease (PD) was defined as at least a 20 percent (%) increase in the sum of diameters of target lesions, taking as reference the smallest sum on study including Baseline. In addition, the sum must also have shown an absolute increase of 5 millimeters (mm). The appearance of one or more new lesions was also considered progression. Analysis of primary endpoints was performed on All randomized participants defined as all participants who were randomized. Participants were grouped according to the treatment to which they were randomized.

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

End point timeframe:

Baseline and every 8 weeks until disease progression, unacceptable toxicity or death until 29 September 2014 (up to approximately 23 months)

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: No statistical analysis was planned for this endpoint. The statistical analysis for progression-free survival is reported in next end point.

| End point values | FOLFIRI+ MEHD7945A | FOLFIRI + Cetuximab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 68 | 66 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 79.4 | 75.8 | | |

### Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Participants With Disease Progression or Death in the HER3-Low Group

| End point title | Percentage of Participants With Disease Progression or Death in |
|---|---|

| | |
|---|---|
| | the HER3-Low Group[2] |

End point description:

HER3 is a protein encoded by the ERBB3 gene. HER3-low participants were identified based on the median ERBB3 expression. Tumor assessments were performed according to modified RECIST v1.1. PD was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study including Baseline. In addition, the sum must also have shown an absolute increase of 5 mm. The appearance of one or more new lesions was also considered progression. Analysis of primary endpoints was performed on All randomized participants defined as all participants who were randomized. Participants were grouped according to the treatment to which they were randomized within the HER3-low expressing group.

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

End point timeframe:

Baseline and every 8 weeks until disease progression, unacceptable toxicity or death until 29 September 2014 (up to approximately 23 months)

Notes:

[2] - 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: No statistical analysis was planned for this endpoint.

| **End point values** | FOLFIRI+ MEHD7945A | FOLFIRI + Cetuximab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 27 | 27 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 77.78 | 85.19 | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Duration of Progression Free Survival (PFS)

| | |
|---|---|
| End point title | Duration of Progression Free Survival (PFS) |

End point description:

PFS was defined as the time from randomization to documented disease progression assessed by the investigator or death, whichever occurred first. PD was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study including Baseline. In addition the sum must also have shown an absolute increase of 5 mm. The appearance of one or more new lesions was also considered progression. Analysis of primary endpoints was performed on all randomized participants and on those with HER3-low tumors.

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

End point timeframe:

Baseline and every 8 weeks until disease progression, unacceptable toxicity or death until Study termination on 29 September 2014 (up to approximately 23 months)

| **End point values** | FOLFIRI+ MEHD7945A | FOLFIRI + Cetuximab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 68 | 66 | | |
| Units: months | | | | |
| median (confidence interval 90%) | 5.4 (3.8 to 7.5) | 5.6 (5.3 to 7.5) | | |

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

Stratification variables included time between last 1L oxaliplatin-containing chemotherapy and disease progression less than or equal to 6 months versus greater than 6 months (<= 6 mo vs > 6 mo) and prior bevacizumab therapy (yes vs no). Hazard ratios were estimated by Cox regression.

| | |
|---|---|
| Comparison groups | FOLFIRI+ MEHD7945A v FOLFIRI + Cetuximab |
| Number of subjects included in analysis | 134 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.198 |
| Method | Logrank |
| Parameter estimate | Log hazard ratio |
| Point estimate | 1.3 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.93 |
| upper limit | 1.82 |

## Primary: Duration of PFS in HER3-Low Group

| End point title | Duration of PFS in HER3-Low Group[3] |
|---|---|

End point description:

HER3 is a protein encoded by the ERBB3 gene. HER3-low participants were identified based on the median ERBB3 expression. PFS was defined as the time from randomization to documented disease progression assessed by the investigator or death, whichever occurred first. PD was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study including Baseline. In addition the sum must also have shown an absolute increase of 5 mm. The appearance of one or more new lesions was also considered progression. Analysis of primary endpoints was performed on all randomized participants and on those with HER3-low tumors.

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

End point timeframe:

Baseline and every 8 weeks until disease progression, unacceptable toxicity or death until Study termination on 29 September 2014 (up to approximately 23 months)

Notes:

[3] - 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: No statistical analysis was planned for this endpoint.

| End point values | FOLFIRI+ MEHD7945A | FOLFIRI + Cetuximab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 27 | 27 | | |
| Units: months | | | | |
| median (confidence interval 90%) | 3.9 (3.7 to 7.5) | 5.5 (3.9 to 5.7) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with Objective Response (Complete Response [CR] or Partial Response [PR])

| End point title | Percentage of Participants with Objective Response (Complete Response [CR] or Partial Response [PR]) |
|---|---|

End point description:

Objective response is defined as a CR or PR, objective responses had to be confirmed ≥ 4 weeks after the initial response. Tumor assessments were performed according to modified RECIST v1.1. CR: Disappearance of all target lesions, and any pathological lymph nodes (whether target or non-target) must have shown a reduction in the short axis to less than (<)10 mm. PR: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. Analysis of secondary outcomes was performed on all randomized participants.

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

End point timeframe:

Baseline and every 8 weeks until Disease progression, Unacceptable Toxicity or Death until Study termination on 29 September 2014 (up to approximately 23 months)

| End point values | FOLFIRI+ MEHD7945A | FOLFIRI + Cetuximab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 68 | 66 | | |
| Units: percentage of partticipants | | | | |
| number (confidence interval 90%) | 16.2 (9.9 to 24.38) | 31.8 (22.41 to 42.23) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of Objective Response

| End point title | Duration of Objective Response |
|---|---|

End point description:

Duration of objective response was defined as the time from the first occurrence of a documented objective response (CR or PR) to documented disease progression or death, whichever occurred first. Analysis was performed on all randomized participants. Time to event was determined using Kaplan-Meier estimates. Confidence Interval (CI) for median was computed using the method of Brookmeyer and Crowley.

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

End point timeframe:

Baseline and every 8 weeks until Disease progression, Unacceptable Toxicity or Death until Study termination on 29 September 2014 (up to approximately 23 months)

| **End point values** | FOLFIRI+ MEHD7945A | FOLFIRI + Cetuximab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 11 | 21 | | |
| Units: months | | | | |
| median (confidence interval 90%) | 7.1 (5.5 to 9.1) | 9 (5.6 to 11) | | |

**Statistical analyses**

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|

Statistical analysis description:

Stratification variables include time between last 1L oxaliplatin-containing chemotherapy and disease progression (<= 6 months vs > 6 months and prior bevacizumab therapy (yes vs no). Hazard ratios were estimated by Cox regression.

| | |
|---|---|
| Comparison groups | FOLFIRI+ MEHD7945A v FOLFIRI + Cetuximab |
| Number of subjects included in analysis | 32 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2185 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.84 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.8 |
| upper limit | 4.22 |

**Secondary: Percentage of Participants Who Died**

| End point title | Percentage of Participants Who Died |
|---|---|

End point description:

Overall survival was defined as the time from randomization to death by any cause.

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

End point timeframe:

Baseline and every 8 weeks until Death (up to approximately 25 months)

| End point values | FOLFIRI+ MEHD7945A | FOLFIRI + Cetuximab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 68 | 66 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 50 | 50 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of Overall Survival

| End point title | Duration of Overall Survival |
|---|---|

End point description:

Overall survival was defined as the time from randomization to death by any cause. Time to event was estimated using Kaplan-Meier estimates. The number "99999" in data field signifies not estimated (NE) data, as the upper limit of 90% CI was not reached in the Kaplan-Meier analysis.

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

End point timeframe:

Baseline and every 8 weeks until Death (up to approximately 25 months)

| End point values | FOLFIRI+ MEHD7945A | FOLFIRI + Cetuximab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 68 | 66 | | |
| Units: months | | | | |
| median (confidence interval 90%) | 14 (11 to 20.3) | 12.4 (10.2 to 99999) | | |

## Statistical analyses

| Statistical analysis title | Statistical Analysis 3 |
|---|---|

Statistical analysis description:

Stratification variables include time between last 1L oxaliplatin-containing chemotherapy and disease progression (<= 6 months vs > 6 months and prior bevacizumab therapy (yes vs no). Hazard ratios were estimated by Cox regression.

| Comparison groups | FOLFIRI + Cetuximab v FOLFIRI+ MEHD7945A |
|---|---|
| Number of subjects included in analysis | 134 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9009 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.97 |

| Confidence interval | |
|---|---|
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.64 |
| upper limit | 1.46 |

## Secondary: Minimum (Cmin) and Maximum (Cmax) Serum Concentrations of MEHD7945A

| End point title | Minimum (Cmin) and Maximum (Cmax) Serum Concentrations of MEHD7945A[4] |
|---|---|

End point description:

Cmax was defined as the maximum or "peak" concentration of MEHD7945A observed after its administration (30 minutes post dose); Cmin was the minimum or "trough" concentration of MEHD7945A (pre dose).

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

End point timeframe:

Pre dose and 30 minutes post dose on Cycle 1 Day 1, Pre dose on Cycle 10 Day 1

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: This endpoint was planned to be reported only in those participants who received MEHD7945A.

| End point values | FOLFIRI+ MEHD7945A | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 66 | | | |
| Units: micrograms per milliliter (µg/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 Cmin | 39.466 (± 43.66) | | | |
| Cycle 1 Cmax | 299.028 (± 66.319) | | | |
| Cycle 10 Cmin | 75.965 (± 42.619) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of participants with anti-MEHD7945A antibodies

| End point title | Percentage of participants with anti-MEHD7945A antibodies |
|---|---|

End point description:

Anti-therapeutic antibodies (ATAs) directed against MEHD7945A were analyzed in serum samples obtained at baseline, before dosing, and at multiple time points (Day 1 of Cycles 1, 4, 8, and at treatment completion) after dosing. Number (n) = number of evaluable participants for the specified category.

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

End point timeframe:

Baseline; Post Baseline (assessed at Day 1 of Cycles 1, 4 and 8 and at study termination on 29 September 2014 [up to approximately 23 months])

| End point values | FOLFIRI+ MEHD7945A | FOLFIRI + Cetuximab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 66 | 17 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Baseline (n=66,4) | 0 | 0 | | |
| Post-baseline treatment induced ATA (n=59,17) | 0 | 0 | | |
| Post-baseline treatment enhanced ATA (n=59,17) | 0 | 0 | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were recorded from the date of randomization until 45 days after study termination (up to approximately 25 months).

| | |
|---|---|
| Assessment type | Non-systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 17.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | FOLFIRI+ MEHD7945A |

Reporting group description:

Participants received MEHD7945A 1100 mg IV infusion every two weeks (14-day cycle) until unacceptable toxicity, documented disease progression or death. Participants also received 5-FU 400 mg/m^2 as an IV bolus and then 5-FU 2400 mg/m^2 as a continuous IV infusion, irinotecan 180 mg/m^2 IV infusion concurrently (using a y connector) with leucovorin 400 mg/m^2 (racemic form) or 200 mg/m^2 (L-isomer form) IV infusion (FOLFIRI) on Day 1 of 14-day continuous cycles. AEs were reported for Safety Evaluable population which included all participants who were randomized and received any amount of study medication.

| | |
|---|---|
| Reporting group title | FOLFIRI + Cetuximab |

Reporting group description:

All participants received cetuximab 400 mg/m^2 initial dose followed by 250 mg/m^2 IV infusion once a week until unacceptable toxicity, documented disease progression or death. Participants also received FOLFIRI on Day 1 of 14-day continuous cycles. AEs were reported for Safety Evaluable population which included all participants who were randomized and received any amount of study medication.

| Serious adverse events | FOLFIRI+ MEHD7945A | FOLFIRI + Cetuximab | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 24 / 67 (35.82%) | 23 / 63 (36.51%) | |
| number of deaths (all causes) | 34 | 33 | |
| number of deaths resulting from adverse events | | | |
| Vascular disorders | | | |
| Vena cava thrombosis | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Device occlusion | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 2 / 63 (3.17%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malaise | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 5 / 67 (7.46%) | 4 / 63 (6.35%) | |
| occurrences causally related to treatment / all | 1 / 6 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombosis in device | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 2 / 63 (3.17%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 4 / 67 (5.97%) | 3 / 63 (4.76%) | |
| occurrences causally related to treatment / all | 3 / 4 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Infusion related reaction | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriospasm coronary | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Convulsions | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 2 / 67 (2.99%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Corneal perforation | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 4 / 63 (6.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 6 / 67 (8.96%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 7 / 7 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal ulcer | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 3 / 63 (4.76%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestinal stenosis | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestinal perforation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Melaena | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mesenteric haematoma | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 2 / 67 (2.99%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 2 / 63 (3.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 67 (4.48%) | 2 / 63 (3.17%) | |
| occurrences causally related to treatment / all | 3 / 3 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholangitis | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Portal vein thrombosis | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Palmar- plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Obstructive uropathy | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Postrenal failure | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure acute | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back pain | | | |
| subjects affected / exposed | 2 / 67 (2.99%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Catheter site cellulitis | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Cellulitis | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 3 / 63 (4.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gangrene | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Localised infection | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Nail bed infection | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 67 (1.49%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Scrotal infection | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 2 / 63 (3.17%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral infection | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Campylobacter infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | FOLFIRI+ MEHD7945A | FOLFIRI + Cetuximab | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 67 / 67 (100.00%) | 63 / 63 (100.00%) | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 43 / 67 (64.18%) | 37 / 63 (58.73%) | |
| occurrences (all) | 64 | 88 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 26 / 67 (38.81%) | 23 / 63 (36.51%) | |
| occurrences (all) | 49 | 40 | |
| Asthenia | | | |
| subjects affected / exposed | 10 / 67 (14.93%) | 9 / 63 (14.29%) | |
| occurrences (all) | 18 | 18 | |
| Pyrexia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 6 / 67 (8.96%) | 11 / 63 (17.46%) | |
| occurrences (all) | 8 | 15 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 5 / 67 (7.46%) | 6 / 63 (9.52%) | |
| occurrences (all) | 5 | 7 | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 4 / 63 (6.35%) | |
| occurrences (all) | 0 | 4 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Epistaxis | | | |
| subjects affected / exposed | 13 / 67 (19.40%) | 8 / 63 (12.70%) | |
| occurrences (all) | 16 | 10 | |
| Dyspnoea | | | |
| subjects affected / exposed | 8 / 67 (11.94%) | 5 / 63 (7.94%) | |
| occurrences (all) | 8 | 8 | |
| Cough | | | |
| subjects affected / exposed | 2 / 67 (2.99%) | 12 / 63 (19.05%) | |
| occurrences (all) | 2 | 13 | |
| Dysphonia | | | |
| subjects affected / exposed | 6 / 67 (8.96%) | 2 / 63 (3.17%) | |
| occurrences (all) | 6 | 2 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 4 / 67 (5.97%) | 3 / 63 (4.76%) | |
| occurrences (all) | 4 | 3 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 3 / 67 (4.48%) | 4 / 63 (6.35%) | |
| occurrences (all) | 3 | 4 | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 5 / 67 (7.46%) | 1 / 63 (1.59%) | |
| occurrences (all) | 5 | 1 | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 4 / 67 (5.97%) | 11 / 63 (17.46%) | |
| occurrences (all) | 4 | 12 | |
| Investigations | | | |

| | | | |
|---|---|---|---|
| Weight decreased | | | |
| subjects affected / exposed | 8 / 67 (11.94%) | 5 / 63 (7.94%) | |
| occurrences (all) | 11 | 5 | |
| Cardiac disorders | | | |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 4 / 63 (6.35%) | |
| occurrences (all) | 1 | 4 | |
| Nervous system disorders | | | |
| Dysgeusia | | | |
| subjects affected / exposed | 11 / 67 (16.42%) | 6 / 63 (9.52%) | |
| occurrences (all) | 15 | 6 | |
| Headache | | | |
| subjects affected / exposed | 10 / 67 (14.93%) | 6 / 63 (9.52%) | |
| occurrences (all) | 10 | 6 | |
| Dizziness | | | |
| subjects affected / exposed | 4 / 67 (5.97%) | 3 / 63 (4.76%) | |
| occurrences (all) | 8 | 3 | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 3 / 67 (4.48%) | 4 / 63 (6.35%) | |
| occurrences (all) | 3 | 6 | |
| Paraesthesia | | | |
| subjects affected / exposed | 2 / 67 (2.99%) | 4 / 63 (6.35%) | |
| occurrences (all) | 2 | 6 | |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 17 / 67 (25.37%) | 21 / 63 (33.33%) | |
| occurrences (all) | 27 | 41 | |
| Anaemia | | | |
| subjects affected / exposed | 9 / 67 (13.43%) | 11 / 63 (17.46%) | |
| occurrences (all) | 14 | 14 | |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 5 / 63 (7.94%) | |
| occurrences (all) | 1 | 9 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 4 / 63 (6.35%) | |
| occurrences (all) | 1 | 5 | |
| Eye disorders | | | |

| | | | |
|---|---|---|---|
| Vision blurred | | | |
| subjects affected / exposed | 5 / 67 (7.46%) | 1 / 63 (1.59%) | |
| occurrences (all) | 5 | 1 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 60 / 67 (89.55%) | 42 / 63 (66.67%) | |
| occurrences (all) | 145 | 107 | |
| Nausea | | | |
| subjects affected / exposed | 33 / 67 (49.25%) | 32 / 63 (50.79%) | |
| occurrences (all) | 49 | 61 | |
| Stomatitis | | | |
| subjects affected / exposed | 21 / 67 (31.34%) | 26 / 63 (41.27%) | |
| occurrences (all) | 34 | 44 | |
| Vomiting | | | |
| subjects affected / exposed | 16 / 67 (23.88%) | 11 / 63 (17.46%) | |
| occurrences (all) | 23 | 27 | |
| Abdominal pain | | | |
| subjects affected / exposed | 12 / 67 (17.91%) | 21 / 63 (33.33%) | |
| occurrences (all) | 18 | 26 | |
| Constipation | | | |
| subjects affected / exposed | 6 / 67 (8.96%) | 16 / 63 (25.40%) | |
| occurrences (all) | 6 | 26 | |
| Gastroesophageal reflux disease | | | |
| subjects affected / exposed | 10 / 67 (14.93%) | 6 / 63 (9.52%) | |
| occurrences (all) | 11 | 7 | |
| Mouth ulceration | | | |
| subjects affected / exposed | 4 / 67 (5.97%) | 4 / 63 (6.35%) | |
| occurrences (all) | 8 | 8 | |
| Oral pain | | | |
| subjects affected / exposed | 7 / 67 (10.45%) | 1 / 63 (1.59%) | |
| occurrences (all) | 8 | 4 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 5 / 67 (7.46%) | 6 / 63 (9.52%) | |
| occurrences (all) | 5 | 6 | |
| Dry mouth | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 4 / 67 (5.97%) | 4 / 63 (6.35%) | |
| occurrences (all) | 6 | 4 | |
| Haemorrhoids | | | |
| subjects affected / exposed | 6 / 67 (8.96%) | 4 / 63 (6.35%) | |
| occurrences (all) | 6 | 4 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 3 / 67 (4.48%) | 5 / 63 (7.94%) | |
| occurrences (all) | 3 | 7 | |
| Cheilitis | | | |
| subjects affected / exposed | 4 / 67 (5.97%) | 1 / 63 (1.59%) | |
| occurrences (all) | 4 | 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 26 / 67 (38.81%) | 32 / 63 (50.79%) | |
| occurrences (all) | 48 | 68 | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 24 / 67 (35.82%) | 22 / 63 (34.92%) | |
| occurrences (all) | 42 | 57 | |
| Alopecia | | | |
| subjects affected / exposed | 18 / 67 (26.87%) | 22 / 63 (34.92%) | |
| occurrences (all) | 19 | 24 | |
| Dry skin | | | |
| subjects affected / exposed | 17 / 67 (25.37%) | 13 / 63 (20.63%) | |
| occurrences (all) | 19 | 19 | |
| Skin fissures | | | |
| subjects affected / exposed | 10 / 67 (14.93%) | 12 / 63 (19.05%) | |
| occurrences (all) | 16 | 18 | |
| Palmar- plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 12 / 67 (17.91%) | 13 / 63 (20.63%) | |
| occurrences (all) | 13 | 20 | |
| Pruritus | | | |
| subjects affected / exposed | 6 / 67 (8.96%) | 7 / 63 (11.11%) | |
| occurrences (all) | 9 | 7 | |
| Rash maculo-papular | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 6 / 67 (8.96%) | 4 / 63 (6.35%) | |
| occurrences (all) | 6 | 5 | |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 4 / 63 (6.35%) | |
| occurrences (all) | 1 | 5 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 8 / 67 (11.94%) | 6 / 63 (9.52%) | |
| occurrences (all) | 10 | 7 | |
| Arthralgia | | | |
| subjects affected / exposed | 6 / 67 (8.96%) | 3 / 63 (4.76%) | |
| occurrences (all) | 9 | 3 | |
| Pain in extremity | | | |
| subjects affected / exposed | 2 / 67 (2.99%) | 6 / 63 (9.52%) | |
| occurrences (all) | 2 | 8 | |
| Muscle spasms | | | |
| subjects affected / exposed | 4 / 67 (5.97%) | 2 / 63 (3.17%) | |
| occurrences (all) | 5 | 2 | |
| Infections and infestations | | | |
| Paronychia | | | |
| subjects affected / exposed | 21 / 67 (31.34%) | 18 / 63 (28.57%) | |
| occurrences (all) | 39 | 34 | |
| Folliculitis | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 8 / 63 (12.70%) | |
| occurrences (all) | 1 | 12 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 7 / 67 (10.45%) | 6 / 63 (9.52%) | |
| occurrences (all) | 7 | 6 | |
| Conjunctivitis | | | |
| subjects affected / exposed | 5 / 67 (7.46%) | 4 / 63 (6.35%) | |
| occurrences (all) | 7 | 5 | |
| Localised infection | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 4 / 63 (6.35%) | |
| occurrences (all) | 0 | 4 | |
| Metabolism and nutrition disorders | | | |

| | | | |
|---|---|---|---|
| Hypokalaemia | | | |
| subjects affected / exposed | 25 / 67 (37.31%) | 13 / 63 (20.63%) | |
| occurrences (all) | 35 | 21 | |
| Decreased appetite | | | |
| subjects affected / exposed | 16 / 67 (23.88%) | 14 / 63 (22.22%) | |
| occurrences (all) | 23 | 23 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 12 / 67 (17.91%) | 23 / 63 (36.51%) | |
| occurrences (all) | 12 | 23 | |
| Dehydration | | | |
| subjects affected / exposed | 9 / 67 (13.43%) | 4 / 63 (6.35%) | |
| occurrences (all) | 10 | 9 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 4 / 67 (5.97%) | 4 / 63 (6.35%) | |
| occurrences (all) | 7 | 8 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 17 July 2012 | The protocol was updated to include two interim safety analyses by the internal monitoring committee (IMC) instead of one interim analysis. The duration of safety monitoring (including reporting of AEs and SAEs) was extended from 30 days to 45 days. Changes were made to Inclusion and Exclusion criteria. |
| 26 April 2013 | Incidence of ATA to MEHD7945A was added as a safety outcome measure.<br>Electrocardiogram (ECG) was added as a safety assessment.<br>The follow-up period for reporting pregnancy was updated to 45 days.<br>Clarification was added to the dosage modification of 1) MEHD7945A, 2) cetuximab and 3) folinic acid |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated on 29 September 2014, following the primary analysis, which indicated that treatment with MEHD7945A FOLFIRI did not improve PFS compared with FOLFIRI cetuximab, by investigator assessment.

Notes: