ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: 06/13/2014

ClinicalTrials.gov ID: NCT00154102

Study Identification

Unique Protocol ID:	EMR 62202-013
Brief Title:	Cetuximab Combined With Irinotecan in First-line Therapy for Metastatic Colorectal Cancer (CRYSTAL)
Official Title:	Open, Randomized, Controlled, Multicenter Phase III Study Comparing 5FU/ FA Plus Irinotecan Plus Cetuximab Versus 5FU/FA Plus Irinotecan as First-line Treatment for Epidermal Growth Factor Receptor-expressing Metastatic Colorectal Cancer
Secondary IDs:	

Study Status

Record Verification:	June 2014
Overall Status:	Completed
Study Start:	May 2004
Primary Completion:	December 2006 [Actual]
Study Completion:	March 2011 [Actual]

Sponsor/Collaborators

Sponsor:	Merck KGaA
Responsible Party:	
Collaborators:	

Oversight

FDA Regulated?:	No
IND/IDE Protocol?:	No

Review Board:	Approval Status: Approved Approval Number: ML2698 Board Name: Commissie Medische Ethiek van de Universitaire Ziekenhuizen KULeuven Board Affiliation: Directoraat Generaal Geneesmiddelenn, Bruxelles Phone: ++32 0 16 34 Email: ec@uzleuven.be
Data Monitoring?:	Yes
Plan to Share Data?:	
Oversight Authorities:	Belgium: Federal Agency for Medicines and Health Products, FAMHP

Study Description

Brief Summary:

Drugs used against cancer work in different ways to stop the growth of tumor cells, either by killing the cells or by stopping them from dividing. Monoclonal antibodies, such as cetuximab, can block tumor growth in different ways. Giving combination chemotherapy together with cetuximab as first treatment after diagnosis of a metastatic colorectal cancer ('1st-line' treatment) may improve the treatment efficacy. However, it is not yet known whether giving combination chemotherapy together with cetuximab is more effective than combination chemotherapy alone. This open-label trial investigates the effectiveness of cetuximab in combination with a standard and effective chemotherapy (5-Fluorouracil (5FU)/Folinic acid (FA) plus irinotecan) for metastatic colorectal cancer in first-line setting, compared to the same chemotherapy alone on patient expressing the epidermal growth factor (EGF) receptor.

Patients expressing this EGF Receptor will be randomly assign in one of the 2 groups to either receive the combination chemotherapy alone or with cetuximab (open-label study) and will then be treated until progression of the disease or unacceptable toxicity occur. Regular efficacy assessments (every 8 weeks) based on imaging will be performed throughout the study together with regular safety assessments (e.g. safety labs). An independent Safety Board of experts will also monitor safety data.

After participant discontinuation from the trial, regular updates on further treatments and survival status will be requested from the investigator.

The entire study (from the first patient entering the study to the last collect of follow-up information) is 4-5 years long.

Detailed Description:

Conditions

Conditions:	Epidermal Growth Factor Receptor (EGFR) Expressing Metastatic Colorectal Cancer
Keywords:	Metastatic colorectal cancer EGFR Irinotecan cetuximab first-line treatment

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Intervention Model:	Parallel Assignment
Number of Arms:	2
Masking:	Open Label
Allocation:	Randomized
Endpoint Classification:	Safety/Efficacy Study
Enrollment:	1221 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Cetuximab Plus FOLFIRI	Drug: Cetuximab Cetuximab intravenous infusion of 400mg/m^2 for the first infusion then weekly intravenous infusion of 250mg/m^2. Number of Cycles: until progression or unacceptable toxicity develops Drug: FOLFIRI (5-Fluorouracil, Folinic acid, Irinotecan) Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops
Active Comparator: FOLFIRI Alone	Drug: FOLFIRI (5-Fluorouracil, Folinic acid, Irinotecan) Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age:	18 Years

Maximum Age:

Gender: Both

Accepts Healthy Volunteers?: No

Criteria: Inclusion Criteria:

- Diagnosis of histologically confirmed adenocarcinoma of the colon or rectum
- Inoperable metastatic disease
- Immunohistochemical evidence of epidermal growth factor receptor expression in tumor tissue
- Presence of at least 1 bi-dimensionally measurable index lesion

Exclusion Criteria:

- Previous irinotecan-based chemotherapy
- Previous chemotherapy for colorectal cancer except adjuvant treatment if terminated more than 6 months before the start of study treatment
- Radiotherapy, surgery (excluding prior diagnostic biopsy) or any investigational drug in the 30 days before the start of study treatment
- Brain metastasis

Contacts/Locations

Study Officials: Eric van Cutsem, Professor
Study Principal Investigator
University Hospital Gasthuisberg, Department Internal Medicine, Leuven, Belgium

Locations: Argentina
Research Site
Buenos Aires, Argentina

Australia
Research Site
Woodville, Australia

Research Site
Bedford Park, Australia

Research Site
West Perth, Australia

Research Site
Nedlands, Australia

Research Site

Darlinghurst, Australia

Austria
Research Site
Wels, Austria

Research Site
St. Pölten, Austria

Research Site
St. Veit an der Glan, Austria

Research Site
Innsbruck, Austria

Research Site
Wien, Austria

Research Site
Salzburg, Austria

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Kufstein, Austria

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Klagenfurt, Austria

Belgium
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Leuven, Belgium

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Bruxelles, Belgium

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Bonheiden, Belgium

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Edegem, Belgium

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Gent, Belgium

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Liège, Belgium

Brazil
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Porto Alegre, Brazil

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Goiania, Brazil

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Santo André, Brazil

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Sao Paulo, Brazil

Bulgaria
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Plovidiv, Bulgaria

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Pleven, Bulgaria

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Varna, Bulgaria

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Sofia, Bulgaria

Chile
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Santiago-Las Condes, Chile

Czech Republic
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Prague, Czech Republic

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Chomutov, Czech Republic

Finland
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Turku, Finland

France
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Boulogne-Billancourt, France

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Villejuif Cedex, France

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Rennes Cedex, France

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Marseille, France

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La Roche sur Yon, France

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Bordeaux, France

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Colmar, France

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Oldenburg, Germany

United Kingdom
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Napoli, Italy

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Benevento, Italy

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Bari, Italy

Korea, Republic of
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Seoul, Korea, Republic of

Mexico
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Roosendaal, Netherlands

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Blaricum, Netherlands

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Den Haag, Netherlands

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Apeldoom, Netherlands

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Zwolle, Netherlands

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Opole, Poland

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Iasi, Romania

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Suceava, Romania

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Cluj Napoca, Romania

Russian Federation
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Saint Petersburg, Russian Federation

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Yaroslavl, Russian Federation

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Trnava, Slovakia

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Pretoria, South Africa

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Cape Town, South Africa

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Barcelona, Spain

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Palma de Mallorca, Spain

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A Coruna, Spain

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Cadiz, Spain

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Göteborg, Sweden

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Stockholm, Sweden

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Chiayi, Taiwan

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Taoyuan, Taiwan

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Taipei, Taiwan

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Changhua, Taiwan

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Krivoy Rog, Ukraine

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Lviv, Ukraine

Research Site
Ivano-Frankivsk, Ukraine

Research Site
Donetsk, Ukraine

Research Site
Charkassy, Ukraine

Australia
Research Site
Heidelberg, Australia

Belgium
Research Site
Antwerpen, Belgium

Chile
Research Site
Santiago-Providencia, Chile

References

Citations: [Study Results] Van Cutsem E, Köhne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, D'Haens G, Pintér T, Lim R, Bodoky G, Roh JK, Folprecht G, Ruff P, Stroh C, Tejpar S, Schlichting M, Nippgen J, Rougier P. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med. 2009 Apr 2;360(14):1408-17. doi: 10.1056/NEJMoa0805019. PubMed 19339720

[Study Results] Van Cutsem E, Lang I, Folprecht G, Nowacki M, Cascinu S, Shchepotin I, Maurel J, Cunningham D, Celik I, Kohne C Cetuximab plus FOLFIRI in the treatment of metastatic colorectal cancer (mCRC): The influence of KRAS and BRAF biomarkers on outcome: Updated data from the CRYSTAL trial. ASCO 2010 Gastrointestinal Cancers Symposium, Orlando, USA January 2010 Abstract No: 281

[Study Results] Lang I, Kohne CH, Folprecht G, Nowacki MP, Cascinu S, Shchepotin I, Maurel J, Cunningham D, Zubel A, Van Cutsem E Cetuximab plus FOLFIRI in 1st-line treatment of metastatic colorectal cancer: Quality of life (QoL) analysis of patients (pts) with KRAS wild-type (wt) tumours in the CRYSTAL trial. European Journal of Cancer Supplements. 2009 7(2):345

Links:

Study Data/Documents:

Study Results

Participant Flow

Recruitment Details	First/Last subject in: 10 Aug 2004/4 Nov 2005. Clinical cut-off efficacy analyses except survival: 27 Jul 2006, Cut off date IRC data: 14 Dec 2006; cut-off safety analyses: 30 Nov 2007; cut-off survival analyses: 31 May 2009; cut-off KRAS analyses: 28 Aug 2009.

	1221 subjects were randomised or treated, of whom 1198 were randomised and treated.
Pre-Assignment Details	At the prescreening visit the subject completed the first informed consent form, and a sample of tumor tissue for determination of EGFR expression was to be obtained. The screening (baseline) visit was performed no more than 21 days before randomization. EGFR-expressing subjects completed a second informed consent form to participate in the study.

Reporting Groups

	Description
Cetuximab Plus FOLFIRI	Cetuximab intravenous infusion of 400mg/m^2 for the first infusion then weekly intravenous infusion of 250mg/m^2. Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops
FOLFIRI Alone	Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops

Overall Study

	Cetuximab Plus FOLFIRI	FOLFIRI Alone
Started	599 [1]	599 [2]
Completed	592	597
Not Completed	7	2
investigational study phase ongoing	7	2

[1] Randomized and treated subjects; 1 additional subject was treated but not randomised
[2] Randomized and treated subjects; 3 additional subjects were treated but not randomised

Baseline Characteristics

Reporting Groups

	Description
Cetuximab Plus FOLFIRI	Cetuximab intravenous infusion of 400mg/m^2 for the first infusion then weekly intravenous infusion of 250mg/m^2. Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops

	Description
FOLFIRI Alone	Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops

Baseline Measures

	Cetuximab Plus FOLFIRI	FOLFIRI Alone	Total
Number of Participants	599	599	1198
Age, Continuous [1] [units: years] Mean (Standard Deviation)	60.0 (10.52)	59.8 (11.06)	59.9 (10.79)
Age, Customized [1] [units: participants]			
Missing	1	0	1
Between 18 and 65 years	374	377	751
>=65 years	224	222	446
Gender, Male/Female [units: participants]			
Female	230	243	473
Male	369	356	725
Region of Enrollment [units: participants]			
Western Europe	262	267	529
Eastern Europe	203	201	404
Rest of the World	134	131	265

[1] Age missing for 1 subject

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Progression-free Survival (PFS) Time - Independent Review Committee (IRC) Assessments

Measure Description	Duration from randomization until radiological progression (based on modified World Health Organisation (WHO) criteria) or death due to any cause. Only deaths within 60 days of last tumor assessment are considered. Patients without event are censored on the date of last tumor assessment.
Time Frame	Time from randomisation to disease progression, death or last tumour assessment, reported between day of first patient randomised, 10 Aug 2004, until cut-off date, 27 July 2006
Safety Issue?	No

Analysis Population Description

Primary analysis on Intent to Treat (ITT) population i.e. all randomized subjects who have received at least one dose of randomized treatment (allocation to treatment groups as randomized).

Reporting Groups

	Description
Cetuximab Plus FOLFIRI	Cetuximab intravenous infusion of 400mg/m^2 for the first infusion then weekly intravenous infusion of 250mg/m^2. Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops
FOLFIRI Alone	Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops

Measured Values

	Cetuximab Plus FOLFIRI	FOLFIRI Alone
Number of Participants Analyzed	599	599
Progression-free Survival (PFS) Time - Independent Review Committee (IRC) Assessments [units: months] Median (95% Confidence Interval)	8.9 (8.0 to 9.4)	8.0 (7.6 to 9.0)

Statistical Analysis 1 for Progression-free Survival (PFS) Time - Independent Review Committee (IRC) Assessments

Statistical Analysis Overview	Comparison Groups	Cetuximab Plus FOLFIRI, FOLFIRI Alone

	Comments	The study was planned with 633 progression events, in order to provide 80% power to test the null hypothesis of no difference in PFS time between treatment groups, assuming a hazard ratio (HR) of 0.8 of cetuximab + chemotherapy (CTX) over CTX alone. Significance level was fixed at 5%. The two-sided stratified log-rank test was employed, considering the randomization strata (region: Western Europe, Eastern Europe, outside Europe and Karnovsky Performance Scale (KPS):<80 vs. ≥80)
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0479
	Comments	[Not specified]
	Method	Other [Stratified log rank]
	Comments	Kaplan-Meier method was used to estimate median PFS time. HR was calculated using Cox proportional hazards model stratified by randomization strata.

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	0.853
	Confidence Interval	(2-Sided) 95% 0.728 to 1.000
	Estimation Comments	[Not specified]

2. Primary Outcome Measure:

Measure Title	Progression-free Survival Time (Chinese V-Ki-ras2 Kirsten Rat Sarcoma Viral Oncogene Homolog (KRAS) Wild-Type Population) - Independent Review Committee (IRC) Assessments
Measure Description	Duration from randomization until radiological progression (based on modified WHO criteria) or death due to any cause. Only deaths within 60 days of last tumor assessment are considered. Patients without event are censored on the date of last tumor assessment.
Time Frame	Time from randomisation to disease progression, death or last tumour assessment, reported between day of first patient randomised, 10 Aug 2004, until cut-off date, 27 July 2006
Safety Issue?	No

Analysis Population Description

Intent to Treat (ITT) population with KRAS Wild Type tumor status as collected until 28 August 2009

Reporting Groups

	Description
Cetuximab Plus FOLFIRI	Cetuximab intravenous infusion of 400mg/m^2 for the first infusion then weekly intravenous infusion of 250mg/m^2. Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops
FOLFIRI Alone	Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops

Measured Values

	Cetuximab Plus FOLFIRI	FOLFIRI Alone
Number of Participants Analyzed	316	350
Progression-free Survival Time (Chinese V-Ki-ras2 Kirsten Rat Sarcoma Viral Oncogene Homolog (KRAS) Wild-Type Population) - Independent Review Committee (IRC) Assessments [units: months] Median (95% Confidence Interval)	9.9 (9.0 to 11.3)	8.4 (7.4 to 9.2)

Statistical Analysis 1 for Progression-free Survival Time (Chinese V-Ki-ras2 Kirsten Rat Sarcoma Viral Oncogene Homolog (KRAS) Wild-Type Population) - Independent Review Committee (IRC) Assessments

Statistical Analysis Overview	Comparison Groups	Cetuximab Plus FOLFIRI, FOLFIRI Alone
	Comments	The two-sided stratified log-rank test was employed at the 5% significance level, considering the randomization strata (region: Western Europe, Eastern Europe, outside Europe and KPS:<80 vs. ≥80)
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0012
	Comments	[Not specified]
	Method	Other [Stratified log rank]
	Comments	Kaplan-Meier method was used to estimate median PFS time. HR was calculated using Cox proportional hazards model stratified by randomization strata.

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	0.696
	Confidence Interval	(2-Sided) 95% 0.558 to 0.867
	Estimation Comments	[Not specified]

3. Primary Outcome Measure:

Measure Title	Progression-free Survival Time (KRAS Mutant Population) - Independent Review Committee (IRC) Assessments
Measure Description	Duration from randomization until radiological progression (based on modified WHO criteria) or death due to any cause. Only deaths within 60 days of last tumor assessment are considered. Patients without event are censored on the date of last tumor assessment.
Time Frame	Time from randomisation to disease progression, death or last tumour assessment, reported between day of first patient randomised, 10 Aug 2004, until cut-off date, 27 July 2006
Safety Issue?	No

Analysis Population Description

Intent to Treat (ITT) population with KRAS Mutant tumor status as collected until 28 August 2009

Reporting Groups

	Description
Cetuximab Plus FOLFIRI	Cetuximab intravenous infusion of 400mg/m^2 for the first infusion then weekly intravenous infusion of 250mg/m^2. Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops
FOLFIRI Alone	Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops

Measured Values

	Cetuximab Plus FOLFIRI	FOLFIRI Alone
Number of Participants Analyzed	214	183
Progression-free Survival Time (KRAS Mutant Population) - Independent Review Committee (IRC) Assessments [units: months] Median (95% Confidence Interval)	7.4 (6.1 to 8.0)	7.7 (7.3 to 9.2)

Statistical Analysis 1 for Progression-free Survival Time (KRAS Mutant Population) - Independent Review Committee (IRC) Assessments

Statistical Analysis Overview	Comparison Groups	Cetuximab Plus FOLFIRI, FOLFIRI Alone
	Comments	The two-sided stratified log-rank test was employed at the 5% significance level, considering the randomization strata (region: Western Europe, Eastern Europe, outside Europe and KPS:<80 vs. ≥80)
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.2648
	Comments	[Not specified]
	Method	Other [Stratified log rank]
	Comments	Kaplan-Meier method was used to estimate median PFS time. HR was calculated using Cox proportional hazards model stratified by randomization strata.
Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	1.171
	Confidence Interval	(2-Sided) 95% 0.887 to 1.544
	Estimation Comments	[Not specified]

4. Secondary Outcome Measure:

Measure Title	Overall Survival Time (OS)
Measure Description	Time from randomization to death. Patients without event are censored at the last date known to be alive or at the clinical cut-off date, whichever is later.
Time Frame	Time from randomisation to death or last day known to be alive, reported between day of first patient randomised, 10 Aug 2004, until cut-off date, 31 May 2009
Safety Issue?	No

Analysis Population Description

ITT population (allocation to treatment groups as randomized and treated)

Reporting Groups

	Description
Cetuximab Plus FOLFIRI	Cetuximab intravenous infusion of 400mg/m^2 for the first infusion then weekly intravenous infusion of 250mg/m^2. Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops
FOLFIRI Alone	Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops

Measured Values

	Cetuximab Plus FOLFIRI	FOLFIRI Alone
Number of Participants Analyzed	599	599
Overall Survival Time (OS) [units: months] Median (95% Confidence Interval)	19.9 (18.5 to 21.3)	18.6 (16.7 to 19.8)

Statistical Analysis 1 for Overall Survival Time (OS)

Statistical Analysis Overview	Comparison Groups	Cetuximab Plus FOLFIRI, FOLFIRI Alone
	Comments	The two-sided stratified log-rank test was employed at the 5% significance level, considering the randomization strata (region: Western Europe, Eastern Europe, outside Europe and KPS:<80 vs. ≥80)
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0419
	Comments	[Not specified]
	Method	Other [Stratified log rank]
	Comments	Kaplan-Meier method was used to estimate median OS time. HR was calculated using Cox proportional hazards model stratified by randomization strata.

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	0.878
	Confidence Interval	(2-Sided) 95%

		0.774 to 0.995
	Estimation Comments	[Not specified]

5. Secondary Outcome Measure:

Measure Title	Overall Survival Time (KRAS Wild-Type Population)
Measure Description	Time from randomization to death. Patients without event are censored at the last date known to be alive or at the clinical cut-off date, whichever is later.
Time Frame	Time from randomisation to death or last day known to be alive reported between day of first patient randomised, 10 Aug 2004, until cut-off date, 31 May 2009
Safety Issue?	No

Analysis Population Description

Intent to Treat (ITT) population with KRAS Wild Type tumor status as collected until 28 August 2009

Reporting Groups

	Description
Cetuximab Plus FOLFIRI	Cetuximab intravenous infusion of 400mg/m^2 for the first infusion then weekly intravenous infusion of 250mg/m^2. Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops
FOLFIRI Alone	Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops

Measured Values

	Cetuximab Plus FOLFIRI	FOLFIRI Alone
Number of Participants Analyzed	316	350
Overall Survival Time (KRAS Wild-Type Population) [units: months] Median (95% Confidence Interval)	23.5 (21.2 to 26.3)	20.0 (17.4 to 21.7)

Statistical Analysis 1 for Overall Survival Time (KRAS Wild-Type Population)

Statistical Analysis Overview	Comparison Groups	Cetuximab Plus FOLFIRI, FOLFIRI Alone

	Comments	The two-sided stratified log-rank test was employed at the 5% significance level, considering the randomization strata (region: Western Europe, Eastern Europe, outside Europe and KPS:<80 vs. ≥80)
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0093
	Comments	[Not specified]
	Method	Other [Stratified log rank]
	Comments	Kaplan-Meier method was used to estimate median OS time. HR was calculated using Cox proportional hazards model stratified by randomization strata.

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	0.796
	Confidence Interval	(2-Sided) 95% 0.670 to 0.946
	Estimation Comments	[Not specified]

6. Secondary Outcome Measure:

Measure Title	Overall Survival Time (KRAS Mutant Population)
Measure Description	Time from randomization to death. Patients without event are censored at the last date known to be alive or at the clinical cut-off date, whichever is later.
Time Frame	Time from randomisation to death or last day known to be alive reported between day of first patient randomised, 10 Aug 2004, until cut-off date, 31 May 2009
Safety Issue?	No

Analysis Population Description

Intent to Treat (ITT) population with KRAS Mutant tumor status as collected until 28 August 2009

Reporting Groups

	Description
Cetuximab Plus FOLFIRI	Cetuximab intravenous infusion of 400mg/m^2 for the first infusion then weekly intravenous infusion of 250mg/m^2. Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops
FOLFIRI Alone	Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops

Measured Values

	Cetuximab Plus FOLFIRI	FOLFIRI Alone
Number of Participants Analyzed	214	183
Overall Survival Time (KRAS Mutant Population) [units: months] Median (95% Confidence Interval)	16.2 (14.9 to 17.9)	16.7 (14.9 to 19.4)

Statistical Analysis 1 for Overall Survival Time (KRAS Mutant Population)

Statistical Analysis Overview	Comparison Groups	Cetuximab Plus FOLFIRI, FOLFIRI Alone
	Comments	The two-sided stratified log-rank test was employed at the 5% significance level, considering the randomization strata (region: Western Europe, Eastern Europe, outside Europe and KPS:<80 vs. ≥80)
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.7549
	Comments	[Not specified]
	Method	Other [Stratified log rank]
	Comments	Kaplan-Meier method was used to estimate median OS time. HR was calculated using Cox proportional hazards model stratified by randomization strata.

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	1.035
	Confidence Interval	(2-Sided) 95%

		0.834 to 1.284
	Estimation Comments	[Not specified]

7. Secondary Outcome Measure:

Measure Title	Best Overall Response Rate - Independent Review Committee (IRC) Assessments
Measure Description	The best overall response rate is defined as the percentage of subjects having achieved confirmed Complete Response + Partial Response as the best overall response according to radiological assessments (based on modified WHO criteria).
Time Frame	evaluations were performed every 6 weeks until progression reported between day of first patient randomised, 10 Aug 2004, until cut-off date, 27 July 2006
Safety Issue?	No

Analysis Population Description

ITT population (allocation to treatment groups as randomized and treated)

Reporting Groups

	Description
Cetuximab Plus FOLFIRI	Cetuximab intravenous infusion of 400mg/m^2 for the first infusion then weekly intravenous infusion of 250mg/m^2. Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops
FOLFIRI Alone	Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops

Measured Values

	Cetuximab Plus FOLFIRI	FOLFIRI Alone
Number of Participants Analyzed	599	599
Best Overall Response Rate - Independent Review Committee (IRC) Assessments [units: percentage of participants] Number (95% Confidence Interval)	46.9 (42.9 to 51.0)	38.7 (34.8 to 42.8)

Statistical Analysis 1 for Best Overall Response Rate - Independent Review Committee (IRC) Assessments

Statistical Analysis Overview	Comparison Groups	Cetuximab Plus FOLFIRI, FOLFIRI Alone
	Comments	The two-sided stratified Cochran-Mantel-Haenszel (CMH) test was employed at the 5% significance level, considering the randomization strata (region: Western Europe, Eastern Europe, outside Europe and KPS:<80 vs. ≥80)
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0038
	Comments	[Not specified]
	Method	Other [Stratified cochran-mantel haenszel test]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	1.40
	Confidence Interval	(2-Sided) 95% 1.12 to 1.77
	Estimation Comments	[Not specified]

8. Secondary Outcome Measure:

Measure Title	Best Overall Response Rate (KRAS Wild-Type Population) - Independent Review Committee (IRC) Assessments
Measure Description	The best overall response rate is defined as the percentage of subjects having achieved confirmed Complete Response + Partial Response as the best overall response according to radiological assessments (based on modified WHO criteria).
Time Frame	evaluations were performed every 6 weeks until progression reported between day of first patient randomised, 10 Aug 2004, until cut-off date, 27 July 2006
Safety Issue?	No

Analysis Population Description

Intent to Treat (ITT) population with KRAS Wild Type tumor status as collected until 28 August 2009

Reporting Groups

	Description
Cetuximab Plus FOLFIRI	Cetuximab intravenous infusion of 400mg/m^2 for the first infusion then weekly intravenous infusion of 250mg/m^2. Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops
FOLFIRI Alone	Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops

Measured Values

	Cetuximab Plus FOLFIRI	FOLFIRI Alone
Number of Participants Analyzed	316	350
Best Overall Response Rate (KRAS Wild-Type Population) - Independent Review Committee (IRC) Assessments [units: percentage participants] Number (95% Confidence Interval)	57.3 (51.6 to 62.8)	39.7 (34.6 to 45.1)

Statistical Analysis 1 for Best Overall Response Rate (KRAS Wild-Type Population) - Independent Review Committee (IRC) Assessments

Statistical Analysis Overview	Comparison Groups	Cetuximab Plus FOLFIRI, FOLFIRI Alone
	Comments	The two-sided stratified Cochran-Mantel-Haenszel (CMH) test was employed at the 5% significance level, considering the randomization strata (region: Western Europe, Eastern Europe, outside Europe and KPS:<80 vs. ≥80)
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	2.069

	Confidence Interval	(2-Sided) 95% 1.515 to 2.826
	Estimation Comments	[Not specified]

9. Secondary Outcome Measure:

Measure Title	Best Overall Response Rate (KRAS Mutant Population) - Independent Review Committee (IRC) Assessments
Measure Description	The best overall response rate is defined as the percentage of subjects having achieved confirmed Complete Response + Partial Response as the best overall response according to radiological assessments (based on modified WHO criteria).
Time Frame	evaluations were performed every 6 weeks until progression reported between day of first patient randomised, 10 Aug 2004, until cut-off date, 27 July 2006
Safety Issue?	No

Analysis Population Description

Intent to Treat (ITT) population with KRAS Mutant tumor status as collected until 28 August 2009

Reporting Groups

	Description
Cetuximab Plus FOLFIRI	Cetuximab intravenous infusion of 400mg/m^2 for the first infusion then weekly intravenous infusion of 250mg/m^2. Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops
FOLFIRI Alone	Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops

Measured Values

	Cetuximab Plus FOLFIRI	FOLFIRI Alone
Number of Participants Analyzed	214	183
Best Overall Response Rate (KRAS Mutant Population) - Independent Review Committee (IRC) Assessments [units: percentage of participants] Number (95% Confidence Interval)	31.3 (25.2 to 38.0)	36.1 (29.1 to 43.5)

Statistical Analysis 1 for Best Overall Response Rate (KRAS Mutant Population) - Independent Review Committee (IRC) Assessments

Statistical Analysis Overview	Comparison Groups	Cetuximab Plus FOLFIRI, FOLFIRI Alone
	Comments	The two-sided stratified Cochran-Mantel-Haenszel (CMH) test was employed at the 5% significance level, considering the randomization strata (region: Western Europe, Eastern Europe, outside Europe and KPS:<80 vs. ≥80)
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.3475
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	0.822
	Confidence Interval	(2-Sided) 95% 0.544 to 1.242
	Estimation Comments	[Not specified]

10. Secondary Outcome Measure:

Measure Title	Disease Control Rate - Independent Review Committee (IRC) Assessments
Measure Description	The disease control rate is defined as the percentage of subjects having achieved confirmed Complete Response + Partial Response + Stable Disease as best overall response according to radiological assessments (based on modified WHO criteria).
Time Frame	Evaluations were performed every 6 weeks until progression reported between day of first patient randomised, 10 Aug 2004, until cut-off date, 27 July 2006
Safety Issue?	No

Analysis Population Description

ITT population (allocation to treatment groups as randomized and treated)

Reporting Groups

	Description
Cetuximab Plus FOLFIRI	Cetuximab intravenous infusion of 400mg/m^2 for the first infusion then weekly intravenous infusion of 250mg/m^2. Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops
FOLFIRI Alone	Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops

Measured Values

	Cetuximab Plus FOLFIRI	FOLFIRI Alone
Number of Participants Analyzed	599	599
Disease Control Rate - Independent Review Committee (IRC) Assessments [units: percentage of participants] Number (95% Confidence Interval)	84.3 (81.1 to 87.1)	85.5 (82.4 to 88.2)

Statistical Analysis 1 for Disease Control Rate - Independent Review Committee (IRC) Assessments

Statistical Analysis Overview	Comparison Groups	Cetuximab Plus FOLFIRI, FOLFIRI Alone
	Comments	The two-sided stratified Cochran-Mantel-Haenszel (CMH) test was employed at the 5% significance level, considering the randomization strata (region: Western Europe, Eastern Europe, outside Europe and KPS:<80 vs. ≥80)
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.6004
	Comments	[Not specified]
	Method	Other [Stratified cochran-mantel haenszel test]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	0.92
	Confidence Interval	(2-Sided) 95%

		0.67 to 1.26
	Estimation Comments	[Not specified]

11. Secondary Outcome Measure:

Measure Title	Duration of Response - Independent Review Committee (IRC) Assessments
Measure Description	Time from first assessment of Complete Response or Partial Response to disease progression or death (within 60 days of last tumor assessment). Patients without event are censored on the date of last tumor assessment. Tumor assessments based on modified WHO criteria.
Time Frame	Time from first assessment of complete response or partial response to disease progression, death or last tumor assessment reported between day of first patient randomised, 10 Aug 2004, until cut-off date, 27 July 2006
Safety Issue?	No

Analysis Population Description

ITT population (allocation to treatment groups as randomized and treated)

Reporting Groups

	Description
Cetuximab Plus FOLFIRI	Cetuximab intravenous infusion of 400mg/m^2 for the first infusion then weekly intravenous infusion of 250mg/m^2. Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops
FOLFIRI Alone	Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops

Measured Values

	Cetuximab Plus FOLFIRI	FOLFIRI Alone
Number of Participants Analyzed	599	599
Duration of Response - Independent Review Committee (IRC) Assessments [units: months] Median (95% Confidence Interval)	9.6 (9.1 to 12.9)	7.7 (6.7 to 8.3)

12. Secondary Outcome Measure:

Measure Title	Participants With No Residual Tumor After Metastatic Surgery
Measure Description	Participants with no residual tumor after on-study surgery for metastases
Time Frame	time from first dose up to 30 days after last dose of study treatment reported between day of first patient randomised, 10 Aug 2004, until cut-off date, 30 Nov 2007
Safety Issue?	No

Analysis Population Description

ITT population (allocation to treatment groups as randomized and treated)

Reporting Groups

	Description
Cetuximab Plus FOLFIRI	Cetuximab intravenous infusion of 400mg/m^2 for the first infusion then weekly intravenous infusion of 250mg/m^2. Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops
FOLFIRI Alone	Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops

Measured Values

	Cetuximab Plus FOLFIRI	FOLFIRI Alone
Number of Participants Analyzed	599	599
Participants With No Residual Tumor After Metastatic Surgery [units: Participants]	29	10

Statistical Analysis 1 for Participants With No Residual Tumor After Metastatic Surgery

Statistical Analysis Overview	Comparison Groups	Cetuximab Plus FOLFIRI, FOLFIRI Alone
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.002
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	3.02
	Confidence Interval	(2-Sided) 95% 1.45 to 6.27
	Estimation Comments	[Not specified]

13. Secondary Outcome Measure:

Measure Title	Quality of Life (QOL) Assessment European Organisation for the Research and Treatment of Cancer (EORTC) QLQ-C30 Global Health Status
Measure Description	Mean global health status scores (EORTC QLQ-C30) against time for each treatment group. Scores were derived from mutually exclusive sets of items, with scale scores ranging from 0 to 100 after a linear transformation. Higher scores indicate a better QoL.
Time Frame	at baseline, at week 8, at week 16, at week 24, at week 32, and at week 40, reported between day of first patient randomised, 10 Aug 2004, until cut-off date, 27 July 2006
Safety Issue?	No

Analysis Population Description

1125 subjects (566 Cetuximab + FOLFIRI; 559 FOLFIRI alone) completed at least 1 evaluable questionnaire & were included in the Evaluable for QLQ-C30 population. Numbers at each timepoint were (Cetuximab + FOLFORI/FOLFORI alone, respectively): baseline 430/423; Week 8 421/390; Week 16 312/309; Week 24 255/244; Week 32 164/154; Week 40 122/96

Reporting Groups

	Description
Cetuximab Plus FOLFIRI	Cetuximab intravenous infusion of 400mg/m^2 for the first infusion then weekly intravenous infusion of 250mg/m^2. Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops
FOLFIRI Alone	Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops

Measured Values

	Cetuximab Plus FOLFIRI	FOLFIRI Alone
Number of Participants Analyzed	566	559
Quality of Life (QOL) Assessment European Organisation for the Research and Treatment of Cancer (EORTC) QLQ-C30 Global Health Status [units: scores on a scale] Least Squares Mean (Standard Error)		
At baseline	58.88 (1.185)	60.33 (1.155)
At week 8	59.02 (1.187)	61.83 (1.176)
At week 16	60.77 (1.276)	63.29 (1.249)
At week 24	61.83 (1.368)	64.06 (1.364)
At week 32	59.68 (1.590)	65.07 (1.612)
At week 40	63.43 (1.835)	64.02 (1.991)

14. Secondary Outcome Measure:

Measure Title	Quality of Life Assessment (EORTC QLQ-C30) Social Functioning
Measure Description	Mean social functioning scores (EORTC QLQ-C30) against time for each treatment group. Scores were derived from mutually exclusive sets of items, with scale scores ranging from 0 to 100 after a linear transformation. Higher scores indicate a higher level of functioning.
Time Frame	at baseline, at week 8, at week 16, at week 24, at week 32, and at week 40, reported between day of first patient randomised, 10 Aug 2004, until cut-off date, 27 July 2006
Safety Issue?	No

Analysis Population Description

1125 subjects (566 in the Cetuximab + FOLFIRI arm and 559 in the FOLFIRI alone arm) completed at least one evaluable QLQ-C30 questionnaire and were thus included in the Evaluable for QLQ-C30 population

Reporting Groups

	Description
Cetuximab Plus FOLFIRI	Cetuximab intravenous infusion of 400mg/m^2 for the first infusion then weekly intravenous infusion of 250mg/m^2. Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops

	Description
FOLFIRI Alone	Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops

Measured Values

	Cetuximab Plus FOLFIRI	FOLFIRI Alone
Number of Participants Analyzed	566	559
Quality of Life Assessment (EORTC QLQ-C30) Social Functioning [units: scores on a scale] Least Squares Mean (Standard Error)		
At baseline	75.21 (1.426)	77.28 (1.395)
At week 8	74.14 (1.430)	76.71 (1.415)
At week 16	73.72 (1.533)	76.67 (1.498)
At week 24	76.31 (1.644)	77.98 (1.633)
At week 32	74.04 (1.903)	75.64 (1.933)
At week 40	76.58 (2.198)	78.07 (2.388)

15. Secondary Outcome Measure:

Measure Title	Safety - Number of Patients Experiencing Any Adverse Event
Measure Description	Please refer to Adverse Events section for further details
Time Frame	time from first dose up to 30 days after last dose of study treatment reported between day of first patient randomised, 10 Aug 2004, until cut-off date, 30 Nov 2007
Safety Issue?	Yes

Analysis Population Description
Safety Population

Reporting Groups

	Description
Cetuximab Plus FOLFIRI	Cetuximab intravenous infusion of 400mg/m^2 for the first infusion then weekly intravenous infusion of 250mg/m^2. Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops
FOLFIRI Alone	Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops

Measured Values

	Cetuximab Plus FOLFIRI	FOLFIRI Alone
Number of Participants Analyzed	600	602
Safety - Number of Patients Experiencing Any Adverse Event [units: participants]	599	597

Reported Adverse Events

Time Frame	Time from first dose up to 30 days after the last dose of study treatment.
Additional Description	Treatment-emergent adverse events were defined as those with onset occurring at or after the first dosing day of study medication and up to 30 days after the last administration of any study drug or the clinical cut-off date.

Reporting Groups

	Description
Cetuximab Plus FOLFIRI	Cetuximab intravenous infusion of 400mg/m^2 for the first infusion then weekly intravenous infusion of 250mg/m^2. Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops. Safety population: includes all treated subjects.

	Description
FOLFIRI Alone	Bi-weekly Irinotecan infusion of 180mg/m^2, Folinic Acid infusion of 400mg/m^2 (racemic) or 200mg/m^2 (L-form), 5-Fluorouracil bolus of 400mg/m^2 followed by a 46-hour continuous infusion of 2400mg/m^2 Number of Cycles: until progression or unacceptable toxicity develops. Safety population: includes all treated subjects

Serious Adverse Events

	Cetuximab Plus FOLFIRI	FOLFIRI Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Total	263/600 (43.83%)	204/602 (33.89%)
Blood and lymphatic system disorders		
ANAEMIA [A] †	2/600 (0.33%)	8/602 (1.33%)
FEBRILE BONE MARROW APLASIA [A] †	1/600 (0.17%)	0/602 (0%)
FEBRILE NEUTROPENIA [A] †	16/600 (2.67%)	13/602 (2.16%)
LEUKOPENIA [A] †	6/600 (1%)	7/602 (1.16%)
LYMPHOPENIA [A] †	1/600 (0.17%)	0/602 (0%)
NEUTROPENIA [A] †	37/600 (6.17%)	35/602 (5.81%)
PANCYTOPENIA [A] †	1/600 (0.17%)	2/602 (0.33%)
PLATELET TOXICITY [A] †	0/600 (0%)	1/602 (0.17%)
THROMBOCYTOPENIA [A] †	3/600 (0.5%)	1/602 (0.17%)
Cardiac disorders		
ACUTE CARDIO-VASCULAR INSUFFICIENCY [A] [1] †	0/600 (0%)	1/602 (0.17%)
ACUTE CORONARY SYNDROME [A] †	0/600 (0%)	1/602 (0.17%)
ACUTE MYOCARDIAL INFARCTION [A] †	3/600 (0.5%)	0/602 (0%)
ANGINA PECTORIS [A] †	2/600 (0.33%)	0/602 (0%)
ARRHYTHMIA [A] †	1/600 (0.17%)	0/602 (0%)

	Cetuximab Plus FOLFIRI	FOLFIRI Alone
	Affected/At Risk (%)	Affected/At Risk (%)
ARRHYTHMIA SUPRAVENTRICULAR [A] †	0/600 (0%)	1/602 (0.17%)
ARTERIOSPASM CORONARY [A] †	0/600 (0%)	1/602 (0.17%)
ATRIAL FIBRILLATION [A] †	3/600 (0.5%)	2/602 (0.33%)
CARDIAC ARREST [A] †	3/600 (0.5%)	1/602 (0.17%)
CARDIAC FAILURE [A] †	1/600 (0.17%)	0/602 (0%)
CARDIAC FAILURE ACUTE [A] †	1/600 (0.17%)	0/602 (0%)
CARDIAC FAILURE CONGESTIVE [A] †	1/600 (0.17%)	0/602 (0%)
CARDIOGENIC SHOCK [A] †	1/600 (0.17%)	0/602 (0%)
CARDIOPULMONARY FAILURE [A] †	1/600 (0.17%)	0/602 (0%)
CIRCULATORY INSUFFICIENCY [A] [1] †	1/600 (0.17%)	0/602 (0%)
CONDUCTION DISORDER [A] †	0/600 (0%)	1/602 (0.17%)
MYOCARDIAL INFARCTION [A] †	3/600 (0.5%)	1/602 (0.17%)
MYOCARDIAL ISCHAEMIA [A] †	3/600 (0.5%)	1/602 (0.17%)
PALPITATIONS [A] †	1/600 (0.17%)	0/602 (0%)
RIGHT VENTRICULAR FAILURE [A] †	0/600 (0%)	1/602 (0.17%)
TACHYCARDIA [A] †	1/600 (0.17%)	0/602 (0%)
Ear and labyrinth disorders		
VERTIGO [A] †	1/600 (0.17%)	0/602 (0%)
Endocrine disorders		
DIABETES INSIPIDUS [A] †	1/600 (0.17%)	0/602 (0%)
Gastrointestinal disorders		
ABDOMINAL HERNIA [A] †	1/600 (0.17%)	0/602 (0%)

	Cetuximab Plus FOLFIRI	FOLFIRI Alone
	Affected/At Risk (%)	Affected/At Risk (%)
ABDOMINAL PAIN [A] †	14/600 (2.33%)	13/602 (2.16%)
ABDOMINAL PAIN UPPER [A] †	3/600 (0.5%)	2/602 (0.33%)
ACUTE ABDOMEN [A] †	0/600 (0%)	1/602 (0.17%)
ANAL FISTULA [A] †	1/600 (0.17%)	0/602 (0%)
ASCITES [A] †	1/600 (0.17%)	3/602 (0.5%)
COLONIC OBSTRUCTION [A] †	1/600 (0.17%)	2/602 (0.33%)
CONSTIPATION [A] †	6/600 (1%)	2/602 (0.33%)
DIARRHOEA [A] †	36/600 (6%)	21/602 (3.49%)
DYSPHAGIA [A] †	1/600 (0.17%)	0/602 (0%)
ENTEROCOLITIS [A] †	1/600 (0.17%)	0/602 (0%)
ENTEROVESICAL FISTULA [A] †	1/600 (0.17%)	0/602 (0%)
GASTRIC ULCER [A] †	1/600 (0.17%)	0/602 (0%)
GASTRO-INTESTINAL FISTULA [A] †	1/600 (0.17%)	0/602 (0%)
GASTROINTESTINAL HAEMORRHAGE [A] †	1/600 (0.17%)	2/602 (0.33%)
GASTROINTESTINAL HYPOMOTILITY [A] †	1/600 (0.17%)	0/602 (0%)
GASTROINTESTINAL OBSTRUCTION [A] †	1/600 (0.17%)	0/602 (0%)
HAEMATEMESIS [A] †	2/600 (0.33%)	0/602 (0%)
HAEMATOCHEZIA [A] †	2/600 (0.33%)	0/602 (0%)
ILEUS [A] †	10/600 (1.67%)	7/602 (1.16%)
ILEUS PARALYTIC [A] †	0/600 (0%)	1/602 (0.17%)
INGUINAL HERNIA [A] †	1/600 (0.17%)	0/602 (0%)

	Cetuximab Plus FOLFIRI	FOLFIRI Alone
	Affected/At Risk (%)	Affected/At Risk (%)
INTESTINAL HAEMORRHAGE [A] †	1/600 (0.17%)	0/602 (0%)
INTESTINAL OBSTRUCTION [A] †	7/600 (1.17%)	8/602 (1.33%)
INTESTINAL PERFORATION [A] †	1/600 (0.17%)	0/602 (0%)
MESENTERIC VEIN THROMBOSIS [A] †	1/600 (0.17%)	0/602 (0%)
NAUSEA [A] †	8/600 (1.33%)	5/602 (0.83%)
PANCREATITIS [A] †	1/600 (0.17%)	0/602 (0%)
PERITONEAL EFFUSION [A] †	0/600 (0%)	1/602 (0.17%)
PERITONITIS [A] †	0/600 (0%)	2/602 (0.33%)
PROCTALGIA [A] †	1/600 (0.17%)	0/602 (0%)
RECTAL HAEMORRHAGE [A] †	0/600 (0%)	4/602 (0.66%)
SMALL INTESTINAL OBSTRUCTION [A] †	2/600 (0.33%)	2/602 (0.33%)
STOMATITIS [A] †	0/600 (0%)	1/602 (0.17%)
SUBILEUS [A] †	2/600 (0.33%)	8/602 (1.33%)
UPPER GASTROINTESTINAL HAEMORRHAGE [A] †	1/600 (0.17%)	0/602 (0%)
VOMITING [A] †	15/600 (2.5%)	16/602 (2.66%)
General disorders		
ASTHENIA [A] †	6/600 (1%)	5/602 (0.83%)
CATHETER RELATED COMPLICATION [A] †	1/600 (0.17%)	2/602 (0.33%)
CATHETER SITE HAEMATOMA [A] †	0/600 (0%)	1/602 (0.17%)
CATHETER SITE INFLAMMATION [A] †	2/600 (0.33%)	0/602 (0%)
CATHETER SITE PAIN [A] †	1/600 (0.17%)	0/602 (0%)

	Cetuximab Plus FOLFIRI	FOLFIRI Alone
	Affected/At Risk (%)	Affected/At Risk (%)
CHEST PAIN [A] †	3/600 (0.5%)	2/602 (0.33%)
CHILLS [A] †	5/600 (0.83%)	2/602 (0.33%)
DEATH [A] †	2/600 (0.33%)	0/602 (0%)
DISEASE PROGRESSION [A] †	1/600 (0.17%)	0/602 (0%)
EXTRAVASATION [A] †	1/600 (0.17%)	0/602 (0%)
FATIGUE [A] †	1/600 (0.17%)	8/602 (1.33%)
GENERAL PHYSICAL HEALTH DETERIORATION [A] †	4/600 (0.67%)	1/602 (0.17%)
INFLAMMATION [A] †	1/600 (0.17%)	0/602 (0%)
INFLUENZA LIKE ILLNESS [A] †	0/600 (0%)	1/602 (0.17%)
INFUSION SITE EXTRAVASATION [A] †	0/600 (0%)	1/602 (0.17%)
INFUSION SITE PAIN [A] †	0/600 (0%)	1/602 (0.17%)
LOCALISED OEDEMA [A] †	1/600 (0.17%)	0/602 (0%)
MUCOSAL INFLAMMATION [A] †	0/600 (0%)	1/602 (0.17%)
MULTI-ORGAN FAILURE [A] †	0/600 (0%)	1/602 (0.17%)
OEDEMA PERIPHERAL [A] †	3/600 (0.5%)	2/602 (0.33%)
PYREXIA [A] †	26/600 (4.33%)	21/602 (3.49%)
THROMBUS//CLOT IN VEIN OF LEFT HAND CAUSING INFECTION [A] [1] †	1/600 (0.17%)	0/602 (0%)
Hepatobiliary disorders		
BILE DUCT STENOSIS [A] †	1/600 (0.17%)	0/602 (0%)
BILIARY FISTULA [A] †	1/600 (0.17%)	0/602 (0%)
CHOLANGITIS [A] †	0/600 (0%)	1/602 (0.17%)

	Cetuximab Plus FOLFIRI	FOLFIRI Alone
	Affected/At Risk (%)	Affected/At Risk (%)
CHOLECYSTITIS [A] †	1/600 (0.17%)	1/602 (0.17%)
CHOLECYSTITIS ACUTE [A] †	0/600 (0%)	1/602 (0.17%)
DILATATION INTRAHEPATIC DUCT ACQUIRED [A] †	0/600 (0%)	1/602 (0.17%)
HEPATIC FAILURE [A] †	1/600 (0.17%)	1/602 (0.17%)
HYPERBILIRUBINAEMIA [A] †	1/600 (0.17%)	1/602 (0.17%)
JAUNDICE [A] †	1/600 (0.17%)	2/602 (0.33%)
Immune system disorders		
ANAPHYLACTIC REACTION [A] †	3/600 (0.5%)	0/602 (0%)
HYPERSENSITIVITY [A] †	4/600 (0.67%)	0/602 (0%)
Infections and infestations		
ABDOMINAL ABSCESS [A] †	1/600 (0.17%)	0/602 (0%)
ABDOMINAL INFECTION [A] †	1/600 (0.17%)	0/602 (0%)
ABSCESS [A] †	1/600 (0.17%)	0/602 (0%)
ABSCESS INTESTINAL [A] †	1/600 (0.17%)	0/602 (0%)
ACUTE GASTROENTERITIS [A] [1] †	0/600 (0%)	1/602 (0.17%)
ACUTE PNEUMONIA [A] [1] †	1/600 (0.17%)	0/602 (0%)
APPENDICITIS [A] †	0/600 (0%)	1/602 (0.17%)
BACTERAEMIA [A] †	0/600 (0%)	1/602 (0.17%)
CATHETER RELATED INFECTION [A] †	8/600 (1.33%)	1/602 (0.17%)
CATHETER SEPSIS [A] †	3/600 (0.5%)	0/602 (0%)
CATHETER SITE INFECTION [A] †	0/600 (0%)	1/602 (0.17%)
CELLULITIS [A] †	3/600 (0.5%)	0/602 (0%)

	Cetuximab Plus FOLFIRI	FOLFIRI Alone
	Affected/At Risk (%)	Affected/At Risk (%)
CENTRAL LINE INFECTION [A] †	10/600 (1.67%)	4/602 (0.66%)
ERYSIPELAS [A] †	1/600 (0.17%)	1/602 (0.17%)
ESCHERICHIA BACTERAEMIA [A] †	1/600 (0.17%)	0/602 (0%)
ESCHERICHIA SEPSIS [A] †	1/600 (0.17%)	0/602 (0%)
GASTROENTERITIS [A] †	1/600 (0.17%)	0/602 (0%)
HERPES ZOSTER [A] †	0/600 (0%)	1/602 (0.17%)
INFECTION [A] †	4/600 (0.67%)	1/602 (0.17%)
INFECTION OF OSTEOSYNTHESIS IN RIGHT ANCLE [A] [1] †	1/600 (0.17%)	0/602 (0%)
LISTERIOSIS [A] †	0/600 (0%)	1/602 (0.17%)
LOWER RESPIRATORY TRACT INFECTION [A] †	2/600 (0.33%)	3/602 (0.5%)
LUNG ABSCESS [A] †	0/600 (0%)	1/602 (0.17%)
NEUTROPENIC INFECTION [A] †	1/600 (0.17%)	0/602 (0%)
NEUTROPENIC SEPSIS [A] †	1/600 (0.17%)	2/602 (0.33%)
OTITIS MEDIA CHRONIC [A] †	1/600 (0.17%)	0/602 (0%)
PELVIC ABSCESS [A] †	0/600 (0%)	1/602 (0.17%)
PERIANAL ABSCESS [A] †	1/600 (0.17%)	0/602 (0%)
PNEUMONIA [A] †	9/600 (1.5%)	7/602 (1.16%)
PNEUMONIA KLEBSIELLA [A] †	1/600 (0.17%)	0/602 (0%)
PNEUMONIA STREPTOCOCCAL [A] †	1/600 (0.17%)	0/602 (0%)
POSTOPERATIVE INFECTION [A] †	1/600 (0.17%)	0/602 (0%)

	Cetuximab Plus FOLFIRI	FOLFIRI Alone
	Affected/At Risk (%)	Affected/At Risk (%)
POSTOPERATIVE WOUND INFECTION [A] †	2/600 (0.33%)	0/602 (0%)
PYELONEPHRITIS [A] †	1/600 (0.17%)	1/602 (0.17%)
PYELONEPHRITIS ACUTE [A] †	0/600 (0%)	1/602 (0.17%)
RESPIRATORY TRACT INFECTION [A] †	0/600 (0%)	1/602 (0.17%)
RETROPERITONEAL ABSCESS [A] †	1/600 (0.17%)	0/602 (0%)
SEPSIS [A] †	4/600 (0.67%)	1/602 (0.17%)
SEPTIC SHOCK [A] †	3/600 (0.5%)	0/602 (0%)
SINUSITIS [A] †	1/600 (0.17%)	0/602 (0%)
SKIN INFECTION [A] †	0/600 (0%)	1/602 (0.17%)
STAPHYLOCOCCAL INFECTION [A] †	0/600 (0%)	1/602 (0.17%)
STAPHYLOCOCCAL SEPSIS [A] †	1/600 (0.17%)	0/602 (0%)
STREPTOCOCCAL SEPSIS [A] †	1/600 (0.17%)	0/602 (0%)
UPPER RESPIRATORY TRACT INFECTION [A] †	3/600 (0.5%)	0/602 (0%)
URINARY TRACT INFECTION [A] †	4/600 (0.67%)	3/602 (0.5%)
VARICELLA [A] †	0/600 (0%)	1/602 (0.17%)
WOUND INFECTION [A] †	1/600 (0.17%)	0/602 (0%)
Injury, poisoning and procedural complications		
ALCOHOL POISONING [A] †	1/600 (0.17%)	0/602 (0%)
ANASTOMOTIC STENOSIS [A] †	0/600 (0%)	1/602 (0.17%)
FALL [A] †	1/600 (0.17%)	1/602 (0.17%)
FEMORAL NECK FRACTURE [A] †	1/600 (0.17%)	0/602 (0%)

	Cetuximab Plus FOLFIRI	FOLFIRI Alone
	Affected/At Risk (%)	Affected/At Risk (%)
FEMUR FRACTURE [A] †	1/600 (0.17%)	0/602 (0%)
FIBULA FRACTURE [A] †	1/600 (0.17%)	0/602 (0%)
FRACTURED SACRUM [A] †	0/600 (0%)	1/602 (0.17%)
HIP FRACTURE [A] †	3/600 (0.5%)	1/602 (0.17%)
INTESTINAL STOMA COMPLICATION [A] †	0/600 (0%)	2/602 (0.33%)
LIMB INJURY [A] †	1/600 (0.17%)	1/602 (0.17%)
OVERDOSE [A] †	1/600 (0.17%)	0/602 (0%)
PATELLA FRACTURE [A] †	0/600 (0%)	1/602 (0.17%)
POST PROCEDURAL BILE LEAK [A] †	1/600 (0.17%)	0/602 (0%)
SPINAL COMPRESSION FRACTURE [A] †	0/600 (0%)	1/602 (0.17%)
STENT OCCLUSION [A] †	0/600 (0%)	1/602 (0.17%)
SUBDURAL HAEMATOMA [A] †	1/600 (0.17%)	0/602 (0%)
VASCULAR ACCESS COMPLICATION [A] †	0/600 (0%)	1/602 (0.17%)
Investigations		
ALANINE AMINOTRANSFERASE INCREASED [A] †	0/600 (0%)	1/602 (0.17%)
BLOOD CREATININE INCREASED [A] †	2/600 (0.33%)	0/602 (0%)
C-REACTIVE PROTEIN INCREASED [A] †	0/600 (0%)	1/602 (0.17%)
HAEMOGLOBIN DECREASED [A] †	0/600 (0%)	1/602 (0.17%)
HEPATIC ENZYME INCREASED [A] †	0/600 (0%)	1/602 (0.17%)
LABORATORY TEST ABNORMAL [A] †	1/600 (0.17%)	0/602 (0%)
NEUTROPHIL COUNT DECREASED [A] †	1/600 (0.17%)	1/602 (0.17%)

	Cetuximab Plus FOLFIRI	FOLFIRI Alone
	Affected/At Risk (%)	Affected/At Risk (%)
PLATELET COUNT DECREASED [A] †	1/600 (0.17%)	0/602 (0%)
URINE ANALYSIS ABNORMAL [A] †	0/600 (0%)	1/602 (0.17%)
WEIGHT DECREASED [A] †	1/600 (0.17%)	0/602 (0%)
WHITE BLOOD CELL COUNT DECREASED [A] †	1/600 (0.17%)	1/602 (0.17%)
Metabolism and nutrition disorders		
ANOREXIA [A] †	4/600 (0.67%)	4/602 (0.66%)
CACHEXIA [A] †	1/600 (0.17%)	1/602 (0.17%)
DEHYDRATION [A] †	16/600 (2.67%)	12/602 (1.99%)
DIABETES MELLITUS [A] †	0/600 (0%)	1/602 (0.17%)
DIABETIC KETOACIDOSIS [A] †	1/600 (0.17%)	0/602 (0%)
ELECTROLYTE IMBALANCE [A] †	1/600 (0.17%)	0/602 (0%)
HYPERGLYCAEMIA [A] †	3/600 (0.5%)	0/602 (0%)
HYPERKALAEMIA [A] †	1/600 (0.17%)	0/602 (0%)
HYPOALBUMINAEMIA [A] †	1/600 (0.17%)	0/602 (0%)
HYPOCALCAEMIA [A] †	3/600 (0.5%)	0/602 (0%)
HYPOGLYCAEMIA [A] †	0/600 (0%)	1/602 (0.17%)
HYPOKALAEMIA [A] †	4/600 (0.67%)	2/602 (0.33%)
HYPOMAGNESAEMIA [A] †	13/600 (2.17%)	1/602 (0.17%)
HYPONATRAEMIA [A] †	0/600 (0%)	1/602 (0.17%)
LACTIC ACIDOSIS [A] †	1/600 (0.17%)	0/602 (0%)
MALNUTRITION [A] †	0/600 (0%)	1/602 (0.17%)

	Cetuximab Plus FOLFIRI	FOLFIRI Alone
	Affected/At Risk (%)	Affected/At Risk (%)
METABOLIC ACIDOSIS [A] †	2/600 (0.33%)	0/602 (0%)
ORAL INTAKE REDUCED [A] †	2/600 (0.33%)	0/602 (0%)
Musculoskeletal and connective tissue disorders		
BACK PAIN [A] †	2/600 (0.33%)	2/602 (0.33%)
JOINT SWELLING [A] †	1/600 (0.17%)	0/602 (0%)
MYALGIA [A] †	0/600 (0%)	1/602 (0.17%)
PAIN IN EXTREMITY [A] †	0/600 (0%)	2/602 (0.33%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
BLADDER NEOPLASM [A] †	1/600 (0.17%)	0/602 (0%)
CANCER PAIN [A] †	0/600 (0%)	1/602 (0.17%)
MALIGNANT NEOPLASM PROGRESSION [A] †	2/600 (0.33%)	0/602 (0%)
METASTASES TO CENTRAL NERVOUS SYSTEM [A] †	2/600 (0.33%)	0/602 (0%)
OVARIAN LOW MALIGNANT POTENTIAL TUMOUR [A] †	1/600 (0.17%)	0/602 (0%)
TUMOUR ASSOCIATED FEVER [A] †	1/600 (0.17%)	0/602 (0%)
TUMOUR HAEMORRHAGE [A] †	1/600 (0.17%)	0/602 (0%)
Nervous system disorders		
CEREBRAL HAEMORRHAGE [A] †	1/600 (0.17%)	0/602 (0%)
CEREBRAL ISCHAEMIA [A] †	2/600 (0.33%)	0/602 (0%)
CEREBROVASCULAR ACCIDENT [A] †	0/600 (0%)	1/602 (0.17%)
COMA [A] †	0/600 (0%)	1/602 (0.17%)
CONVULSION [A] †	1/600 (0.17%)	0/602 (0%)

	Cetuximab Plus FOLFIRI	FOLFIRI Alone
	Affected/At Risk (%)	Affected/At Risk (%)
COORDINATION ABNORMAL [A] †	0/600 (0%)	1/602 (0.17%)
DEPRESSED LEVEL OF CONSCIOUSNESS [A] †	0/600 (0%)	1/602 (0.17%)
DIZZINESS [A] †	2/600 (0.33%)	0/602 (0%)
EPILEPSY [A] †	1/600 (0.17%)	1/602 (0.17%)
HEADACHE [A] †	1/600 (0.17%)	0/602 (0%)
HEMIPARESIS [A] †	2/600 (0.33%)	0/602 (0%)
LETHARGY [A] †	0/600 (0%)	1/602 (0.17%)
LOSS OF CONSCIOUSNESS [A] †	2/600 (0.33%)	0/602 (0%)
PARAESTHESIA [A] †	0/600 (0%)	1/602 (0.17%)
SOMNOLENCE [A] †	1/600 (0.17%)	0/602 (0%)
SPINAL CORD COMPRESSION [A] †	1/600 (0.17%)	0/602 (0%)
SYNCOPE [A] †	2/600 (0.33%)	2/602 (0.33%)
TRANSIENT ISCHAEMIC ATTACK [A] †	0/600 (0%)	1/602 (0.17%)
VOCAL CORD PARALYSIS [A] †	0/600 (0%)	1/602 (0.17%)
Psychiatric disorders		
ABNORMAL BEHAVIOUR [A] †	0/600 (0%)	1/602 (0.17%)
CONFUSIONAL STATE [A] †	1/600 (0.17%)	2/602 (0.33%)
EUPHORIC MOOD [A] †	1/600 (0.17%)	0/602 (0%)
MENTAL STATUS CHANGES [A] †	1/600 (0.17%)	0/602 (0%)
Renal and urinary disorders		
CALCULUS URETERIC [A] †	2/600 (0.33%)	0/602 (0%)
CALCULUS URINARY [A] †	1/600 (0.17%)	0/602 (0%)

	Cetuximab Plus FOLFIRI	FOLFIRI Alone
	Affected/At Risk (%)	Affected/At Risk (%)
DYSURIA [A] †	1/600 (0.17%)	1/602 (0.17%)
HAEMATURIA [A] †	0/600 (0%)	1/602 (0.17%)
HAEMORRHAGE URINARY TRACT [A] †	1/600 (0.17%)	0/602 (0%)
HYDRONEPHROSIS [A] †	1/600 (0.17%)	1/602 (0.17%)
NEPHROLITHIASIS [A] †	0/600 (0%)	1/602 (0.17%)
RENAL COLIC [A] †	0/600 (0%)	1/602 (0.17%)
RENAL FAILURE [A] †	2/600 (0.33%)	1/602 (0.17%)
RENAL FAILURE ACUTE [A] †	1/600 (0.17%)	1/602 (0.17%)
URETERIC OBSTRUCTION [A] †	2/600 (0.33%)	1/602 (0.17%)
URINARY RETENTION [A] †	1/600 (0.17%)	1/602 (0.17%)
VAGINAL HAEMORRHAGE [A] †	1/600 (0.17%)	0/602 (0%)
Reproductive system and breast disorders		
BENIGN PROSTATIC HYPERPLASIA [A] †	0/600 (0%)	1/602 (0.17%)
Respiratory, thoracic and mediastinal disorders		
ASTHMA [A] †	1/600 (0.17%)	0/602 (0%)
BRONCHOSPASM [A] †	0/600 (0%)	1/602 (0.17%)
CHRONIC OBSTRUCTIVE PULMONARY DISEASE [A] †	0/600 (0%)	1/602 (0.17%)
DYSPNOEA [A] †	7/600 (1.17%)	4/602 (0.66%)
PLEURAL EFFUSION [A] †	3/600 (0.5%)	0/602 (0%)
PLEURITIC PAIN [A] †	2/600 (0.33%)	0/602 (0%)
PULMONARY EMBOLISM [A] †	20/600 (3.33%)	10/602 (1.66%)
PULMONARY OEDEMA [A] †	1/600 (0.17%)	0/602 (0%)

	Cetuximab Plus FOLFIRI	FOLFIRI Alone
	Affected/At Risk (%)	Affected/At Risk (%)
RESPIRATORY FAILURE [A] †	2/600 (0.33%)	1/602 (0.17%)
Skin and subcutaneous tissue disorders		
ACNE [A] †	2/600 (0.33%)	0/602 (0%)
DERMATITIS ACNEIFORM [A] †	1/600 (0.17%)	0/602 (0%)
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME [A] †	1/600 (0.17%)	1/602 (0.17%)
RASH [A] †	1/600 (0.17%)	0/602 (0%)
Surgical and medical procedures		
CATARACT OPERATION [A] †	1/600 (0.17%)	0/602 (0%)
Vascular disorders		
AXILLARY VEIN THROMBOSIS [A] †	1/600 (0.17%)	0/602 (0%)
CIRCULATORY COLLAPSE [A] †	1/600 (0.17%)	0/602 (0%)
DEEP VEIN THROMBOSIS [A] †	9/600 (1.5%)	5/602 (0.83%)
EMBOLISM [A] †	0/600 (0%)	1/602 (0.17%)
HYPERTENSION [A] †	1/600 (0.17%)	0/602 (0%)
HYPOTENSION [A] †	5/600 (0.83%)	3/602 (0.5%)
INTERMITTENT CLAUDICATION [A] †	0/600 (0%)	1/602 (0.17%)
ISCHAEMIA [A] †	0/600 (0%)	1/602 (0.17%)
JUGULAR VEIN THROMBOSIS [A] †	1/600 (0.17%)	0/602 (0%)
PERIPHERAL ISCHAEMIA [A] †	0/600 (0%)	1/602 (0.17%)
PERIPHERAL OCCLUSIVE DISEASE [A] †	1/600 (0.17%)	0/602 (0%)
PHLEBITIS [A] †	0/600 (0%)	1/602 (0.17%)

	Cetuximab Plus FOLFIRI	FOLFIRI Alone
	Affected/At Risk (%)	Affected/At Risk (%)
SUBCLAVIAN VEIN THROMBOSIS [A] †	0/600 (0%)	1/602 (0.17%)
THROMBOSIS [A] †	4/600 (0.67%)	4/602 (0.66%)
VENA CAVA THROMBOSIS [A] †	1/600 (0.17%)	0/602 (0%)
VENOUS THROMBOSIS [A] †	2/600 (0.33%)	1/602 (0.17%)
VENOUS THROMBOSIS LIMB [A] †	1/600 (0.17%)	0/602 (0%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 10.0

[1] An organ system was assigned to this adverse event as required for posting on Clinicaltrials.gov - the organ system was not assigned in the Clinical Study Report

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Cetuximab Plus FOLFIRI	FOLFIRI Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Total	593/600 (98.83%)	591/602 (98.17%)
Blood and lymphatic system disorders		
ANAEMIA [A] †	121/600 (20.17%)	127/602 (21.1%)
LEUKOPENIA [A] †	127/600 (21.17%)	120/602 (19.93%)
LYMPHOPENIA [A] †	29/600 (4.83%)	35/602 (5.81%)
NEUTROPENIA [A] †	272/600 (45.33%)	249/602 (41.36%)
THROMBOCYTOPENIA [A] †	31/600 (5.17%)	20/602 (3.32%)
Eye disorders		
CONJUNCTIVITIS [A] †	88/600 (14.67%)	13/602 (2.16%)
Gastrointestinal disorders		
ABDOMINAL PAIN [A] †	142/600 (23.67%)	154/602 (25.58%)
ABDOMINAL PAIN UPPER [A] †	45/600 (7.5%)	33/602 (5.48%)

	Cetuximab Plus FOLFIRI	FOLFIRI Alone
	Affected/At Risk (%)	Affected/At Risk (%)
CONSTIPATION [A] †	135/600 (22.5%)	119/602 (19.77%)
DIARRHOEA [A] †	377/600 (62.83%)	353/602 (58.64%)
DYSPEPSIA [A] †	78/600 (13%)	46/602 (7.64%)
NAUSEA [A] †	322/600 (53.67%)	359/602 (59.63%)
STOMATITIS [A] †	169/600 (28.17%)	110/602 (18.27%)
VOMITING [A] †	194/600 (32.33%)	231/602 (38.37%)
General disorders		
ASTHENIA [A] †	110/600 (18.33%)	112/602 (18.6%)
FATIGUE [A] †	192/600 (32%)	186/602 (30.9%)
INJECTION SITE REACTION [A] †	40/600 (6.67%)	38/602 (6.31%)
MUCOSAL INFLAMMATION [A] †	82/600 (13.67%)	53/602 (8.8%)
OEDEMA PERIPHERAL [A] †	48/600 (8%)	42/602 (6.98%)
PYREXIA [A] †	136/600 (22.67%)	64/602 (10.63%)
Infections and infestations		
NASOPHARYNGITIS [A] †	30/600 (5%)	35/602 (5.81%)
PARONYCHIA [A] †	107/600 (17.83%)	3/602 (0.5%)
Investigations		
WEIGHT DECREASED [A] †	94/600 (15.67%)	52/602 (8.64%)
Metabolism and nutrition disorders		
ANOREXIA [A] †	169/600 (28.17%)	149/602 (24.75%)
HYPOKALAEMIA [A] †	58/600 (9.67%)	30/602 (4.98%)
HYPOMAGNESAEMIA [A] †	42/600 (7%)	3/602 (0.5%)
Musculoskeletal and connective tissue disorders		

	Cetuximab Plus FOLFIRI	FOLFIRI Alone
	Affected/At Risk (%)	Affected/At Risk (%)
BACK PAIN [A] †	38/600 (6.33%)	55/602 (9.14%)
PAIN IN EXTREMITY [A] †	30/600 (5%)	23/602 (3.82%)
Nervous system disorders		
DIZZINESS [A] †	43/600 (7.17%)	40/602 (6.64%)
DYSGEUSIA [A] †	41/600 (6.83%)	45/602 (7.48%)
HEADACHE [A] †	64/600 (10.67%)	55/602 (9.14%)
Psychiatric disorders		
INSOMNIA [A] †	57/600 (9.5%)	53/602 (8.8%)
Respiratory, thoracic and mediastinal disorders		
COUGH [A] †	64/600 (10.67%)	59/602 (9.8%)
DYSPNOEA [A] †	53/600 (8.83%)	32/602 (5.32%)
EPISTAXIS [A] †	50/600 (8.33%)	27/602 (4.49%)
Skin and subcutaneous tissue disorders		
ACNE [A] †	69/600 (11.5%)	1/602 (0.17%)
ALOPECIA [A] †	224/600 (37.33%)	229/602 (38.04%)
DERMATITIS ACNEIFORM [A] †	146/600 (24.33%)	2/602 (0.33%)
DRY SKIN [A] †	133/600 (22.17%)	30/602 (4.98%)
ERYTHEMA [A] †	40/600 (6.67%)	12/602 (1.99%)
EXFOLIATIVE RASH [A] †	35/600 (5.83%)	3/602 (0.5%)
NAIL DISORDER [A] †	54/600 (9%)	5/602 (0.83%)
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME [A] †	101/600 (16.83%)	27/602 (4.49%)

	Cetuximab Plus FOLFIRI	FOLFIRI Alone
	Affected/At Risk (%)	Affected/At Risk (%)
PRURITUS [A] †	73/600 (12.17%)	28/602 (4.65%)
RASH [A] †	270/600 (45%)	23/602 (3.82%)
SKIN FISSURES [A] †	97/600 (16.17%)	10/602 (1.66%)
SKIN TOXICITY [A] †	34/600 (5.67%)	1/602 (0.17%)
Vascular disorders		
HYPERTENSION [A] †	46/600 (7.67%)	36/602 (5.98%)
HYPOTENSION [A] †	32/600 (5.33%)	20/602 (3.32%)
PHLEBITIS [A] †	38/600 (6.33%)	20/602 (3.32%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 10.0

Limitations and Caveats

A non-specific outcome measure 'Safety' was deleted from the entry in error. A replacement outcome was created. The outcome refers to adverse events.

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

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