ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: 08/05/2014

ClinicalTrials.gov ID: NCT00125034

Study Identification

Unique Protocol ID:	EMR 62202-047
Brief Title:	Oxaliplatin and Cetuximab in First-line Treatment of Metastatic Colorectal Cancer (mCRC) (OPUS)
Official Title:	Open, Randomized, Controlled, Multicenter Phase II Study Comparing 5-FU/FA Plus Oxaliplatin (FOLFOX-4) Plus Cetuximab Versus 5-FU/FA Plus Oxaliplatin (FOLFOX-4) as First-line Treatment for Epidermal Growth Factor Receptor-expressing Metastatic Colorectal Cancer
Secondary IDs:	

Study Status

Record Verification:	August 2011
Overall Status:	Completed
Study Start:	July 2005
Primary Completion:	March 2007 [Actual]
Study Completion:	November 2010 [Actual]

Sponsor/Collaborators

Sponsor:	Merck KGaA
Responsible Party:	Sponsor
Collaborators:	

Oversight

FDA Regulated?:	No

IND/IDE Protocol?:	No
Review Board:	Approval Status: Approved Approval Number: 2468 Board Name: Ethik-Kommission der Ärztekammer Hamburg Board Affiliation: Landesärztekammer (District Physician Chamber) Phone: +49-40-22802 Email: ethik@aerztekammer-hamburg.de
Data Monitoring?:	No
Plan to Share Data?:	
Oversight Authorities:	Germany: Federal Institute for Drugs and Medical Devices

Study Description

Brief Summary:	This is an open label, randomized, controlled, multicenter phase II study comparing 5-FU/FA + oxaliplatin (FOLFOX-4) + cetuximab versus 5-FU/FA + oxaliplatin as first-line treatment for epidermal growth factor receptor (EGFR)-expressing mCRC.
Detailed Description:	

Conditions

Conditions:	Neoplasm Metastasis Colorectal Cancer
Keywords:	FOLFOX-4 Cetuximab First-line mCRC EGFR positive metastatic CRC first-line MCRC EGFR positive metastatic CRC

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 2
Intervention Model:	Parallel Assignment

Number of Arms:	2
Masking:	Open Label
Allocation:	Randomized
Endpoint Classification:	Efficacy Study
Enrollment:	344 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Cetuximab Plus FOLFOX-4	Biological/Vaccine: Cetuximab Cetuximab will always be administered first, followed by oxaliplatin at least 1 hour later. Following completion of the oxaliplatin infusion or simultaneously with oxaliplatin folinic acid (FA) will be administered (at a dose of 200 mg/m^2, infused over 120 minutes, on day 1 and day 2, every two weeks) and then 5-Fluorouracil (5-FU) (as a bolus of 400 mg/m^2/day intravenously (IV) over 2-4 minutes followed by 600 mg/m^2/day infused over 22-hour, on day 1 and day 2, every two weeks). Until progression or unacceptable toxicity develops
Active Comparator: FOLFOX-4 Alone	Drug: Oxaliplatin Oxaliplatin will always be administered first or simultaneously with FA (at a dose of 200 mg/m^2, infused over 120 minutes, on day 1 and day 2, every two weeks) and then 5-FU (as a bolus of 400 mg/m^2/day IV over 2-4 minutes followed by 600 mg/m^2/day infused over 22-hour, on day 1 and day 2, every two weeks). 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:

- First-line mCRC

- EGFR positive
- Bi-dimensional measurable index lesion

Exclusion Criteria:

- Previous exposure to EGFR-targeting therapy
- Previous oxaliplatin-based therapy
- Previous chemotherapy for colorectal cancer except adjuvant treatment with progression of disease documented > 6 months after end of adjuvant treatment
- Radiotherapy
- Surgery
- Any other investigational drug in the 30 days before randomization
- Brain metastasis and/or leptomeningeal disease
- Acute or sub-acute intestinal occlusion or history of inflammatory bowel disease

Contacts/Locations

Study Officials: Bokemeyer, Prof. Dr.
Study Principal Investigator
Klinik für Onkologie, Hämatologie und Knochenmarktransplantationen Universitätsklinikum Hamburg-Eppendorf, Germany

Locations: Austria
Research Site
Wien, Austria

Research Site
Linz, Austria

Research Site
Zams, Austria

Research Site
Graz, Austria

Belgium
Research Site
Hasselt, Belgium

Research Site
Antwerpen, Belgium

Research Site
Turnhout, Belgium

Research Site

Brugge, Belgium

France
Research Site
Besancon, France

Research Site
Clermond Ferrand, France

Research Site
Paris, France

Research Site
Rouen, France

Research Site
Clichy, France

Research Site
Strasbourg, France

Research Site
Montpellier, France

Germany
Research Site
Hamburg, Germany

Research Site
Aschaffenburg, Germany

Research Site
Tübingen, Germany

Research Site
Magdeburg, Germany

Research Site
Essen, Germany

Research Site
Nürnberg, Germany

Research Site
Mannheim, Germany

Greece
Research Site
Athens, Greece

Research Site
Loannina, Greece

Research Site
Thessaloniki, Greece

Italy
Research Site
Milano, Italy

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Rome, Italy

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Torino, Italy

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Pavia, Italy

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Padova, Italy

Research Site
Brescia, Italy

Poland
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Warszawa, Poland

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Szczecin, Poland

Research Site
Poznan, Poland

Research Site
Bialystok, Poland

Research Site
Lublin, Poland

Research Site

Krakow, Poland

Portugal
Research Site
Lisbon, Portugal

Research Site
Santa Maira da Feira, Portugal

Romania
Research Site
Bucurest, Romania

Research Site
Alba Iulia, Romania

Research Site
Onesti, Romania

Research Site
Timisoara, Romania

Research Site
Oradea, Romania

Russian Federation
Research Site
Moscow, Russian Federation

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Samara, Russian Federation

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Kazan, Russian Federation

Research Site
Krasnodar, Russian Federation

Research Site
St. Petersburg, Russian Federation

Research Site
Obninsk, Russian Federation

Spain
Research Site

Bilbao, Spain

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Girona, Spain

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Reus, Spain

Research Site
Valencia, Spain

Research Site
Burgos, Spain

Research Site
Malaga, Spain

Research Site
Orense, Spain

Research Site
Madrid, Spain

Ukraine
Research Site
Dnepropetrovsk, Ukraine

Research Site
Kharkov, Ukraine

Research Site
Vinnitsa, Ukraine

Research Site
Simferopol, Ukraine

Austria
Research Site
Salzburg, Austria

Belgium
Research Site
Roeselare, Belgium

Research Site
ZU Gent, Belgium

Germany
Research Site
Kiel, Germany

Research Site
Dresden, Germany

Israel
Research Site
Tel-Aviv, Israel

Research Site
Haifa, Israel

Research Site
Petah Tiqva, Israel

Research Site
Tel-Hashomer, Israel

Research Site
Kfar-Saba, Israel

Research Site
Rehovot, Israel

Belgium
Research Site
Leuven, Belgium

Research Site
Bonheiden, Belgium

Poland
Research Site
Opole, Poland

Ukraine
Research Site
Kiev, Ukraine

Research Site
Lviv, Ukraine

References

Citations: [Study Results] Bokemeyer C, Bondarenko I, Makhson A, Hartmann JT, Aparicio J, de Braud F, Donea S, Ludwig H, Schuch G, Stroh C, Loos AH, Zubel A, Koralewski P. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. J Clin Oncol. 2009 Feb 10;27(5):663-71. doi: 10.1200/JCO.2008.20.8397. Epub 2008 Dec 29. PubMed 19114683

[Study Results] Bokemeyer C, Bondarenko I, Hartmann JT, de Braud F, Schuch G, Zubel A, Celik I, Schlichting M, Koralewski P. Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal cancer: the OPUS study. Ann Oncol. 2011 Jul;22(7):1535-46. doi: 10.1093/annonc/mdq632. Epub 2011 Jan 12. PubMed 21228335

Links:

Study Data/Documents:

Study Results

Participant Flow

Recruitment Details	First & last subject randomized: 27 Jul 2005 & 8 Mar 2006, respectively. Primary outcome and disease control rate cut-off dates 4 Aug 2006, others: 1 Mar 2007; except overall survival, KRAS overall survival and KRAS progression-free survival outcomes, metastatic surgery outcome and adverse events: 30 Nov 2008.
Pre-Assignment Details	629 subjects were prescreened, of whom 344 subjects were randomised. 338 subjects (Safety Population) received treatment. One subject was erroneously randomized, and was excluded from the ITT population (337 subjects).

Reporting Groups

	Description
Cetuximab Plus FOLFOX-4	Cetuximab plus 5-Fluorouracil(5-FU)/Folinic acid (FA) and oxaliplatin. Cetuximab will always be administered first, followed by oxaliplatin at least 1 hour later. Following completion of the oxaliplatin infusion or simultaneously with oxaliplatin FA will be administered (at a dose of 200 mg/m^2, infused over 120 minutes, on day 1 and day 2, every two weeks) and then 5-FU (as a bolus of 400 mg/m^2/day intravenously (IV) over 2-4 minutes followed by 600 mg/m^2/day infused over 22-hour, on day 1 and day 2, every two weeks). Until progression or unacceptable toxicity develops. Safety population: includes all treated subjects.
FOLFOX-4 Alone	5-FU/FA and oxaliplatin. Oxaliplatin will always be administered first or simultaneously with FA (at a dose of 200 mg/m^2, infused over 120 minutes, on day 1 and day 2, every two weeks) and then 5-FU (as a bolus of 400 mg/m^2/day IV over 2-4 minutes followed by 600 mg/m^2/day infused over 22-hour, on day 1 and day 2, every two weeks). Until progression or unacceptable toxicity develops. Safety population: includes all treated subjects.

Overall Study

	Cetuximab Plus FOLFOX-4	FOLFOX-4 Alone
Started	170 [1]	168 [2]
Completed	170	168
Not Completed	0	0

[1] Randomized & treated. 1 subject was not randomized correctly and was excluded in the ITT population.
[2] Randomized & treated

Baseline Characteristics

Reporting Groups

	Description
Cetuximab Plus FOLFOX-4	Cetuximab plus 5-Fluorouracil(5-FU)/Folinic acid (FA) and oxaliplatin. Cetuximab will always be administered first, followed by oxaliplatin at least 1 hour later. Following completion of the oxaliplatin infusion or simultaneously with oxaliplatin FA will be administered (at a dose of 200 mg/m^2, infused over 120 minutes, on day 1 and day 2, every two weeks) and then 5-FU (as a bolus of 400 mg/m^2/day intravenously (IV) over 2-4 minutes followed by 600 mg/m^2/day infused over 22-hour, on day 1 and day 2, every two weeks). Until progression or unacceptable toxicity develops. Safety population: includes all treated subjects.
FOLFOX-4 Alone	5-FU/FA and oxaliplatin. Oxaliplatin will always be administered first or simultaneously with FA (at a dose of 200 mg/m^2, infused over 120 minutes, on day 1 and day 2, every two weeks) and then 5-FU (as a bolus of 400 mg/m^2/day IV over 2-4 minutes followed by 600 mg/m^2/day infused over 22-hour, on day 1 and day 2, every two weeks). Until progression or unacceptable toxicity develops. Safety population: includes all treated subjects.

Baseline Measures

	Cetuximab Plus FOLFOX-4	FOLFOX-4 Alone	Total
Number of Participants	169	168	337
Age, Categorical [units: participants]			
<=18 years	0	0	0
Between 18 and 65 years	96	109	205
>=65 years	73	59	132

	Cetuximab Plus FOLFOX-4	FOLFOX-4 Alone	Total
Age, Continuous [units: years] Median (Full Range)	62.0 (24 to 82)	60.0 (30 to 82)	61.0 (24 to 82)
Gender, Male/Female [units: participants]			
Female	80	76	156
Male	89	92	181
Region of Enrollment [1] [units: participants]			
Portugal	0	3	3
Spain	19	16	35
Ukraine	24	25	49
Austria	16	9	25
Russian Federation	25	24	49
Israel	0	1	1
Italy	8	6	14
France	3	12	15
Belgium	12	6	18
Poland	30	31	61
Romania	18	13	31
Germany	14	22	36

[1] Figures refer to randomized and treated participants

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Best Overall Response Rate - Independent Review Committee (IRC)
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 World Health Organisation (WHO) criteria) as assessed by an IRC.

Time Frame	Evaluations were performed every 6 weeks until progression, reported between day of first patient randomised, 27 Jul 2005, until cut-off date 4 August 2006
Safety Issue?	No

Analysis Population Description

Primary analysis on the 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 FOLFOX-4	Cetuximab plus 5-Fluorouracil(5-FU)/Folinic acid (FA) and oxaliplatin. Cetuximab will always be administered first, followed by oxaliplatin at least 1 hour later. Following completion of the oxaliplatin infusion or simultaneously with oxaliplatin FA will be administered (at a dose of 200 mg/m^2, infused over 120 minutes, on day 1 and day 2, every two weeks) and then 5-FU (as a bolus of 400 mg/m^2/day intravenously (IV) over 2-4 minutes followed by 600 mg/m^2/day infused over 22-hour, on day 1 and day 2, every two weeks). Until progression or unacceptable toxicity develops. Safety population: includes all treated subjects.
FOLFOX-4 Alone	5-FU/FA and oxaliplatin. Oxaliplatin will always be administered first or simultaneously with FA (at a dose of 200 mg/m^2, infused over 120 minutes, on day 1 and day 2, every two weeks) and then 5-FU (as a bolus of 400 mg/m^2/day IV over 2-4 minutes followed by 600 mg/m^2/day infused over 22-hour, on day 1 and day 2, every two weeks). Until progression or unacceptable toxicity develops. Safety population: includes all treated subjects.

Measured Values

	Cetuximab Plus FOLFOX-4	FOLFOX-4 Alone
Number of Participants Analyzed	169	168
Best Overall Response Rate - Independent Review Committee (IRC) [units: percentage of participants] Number (95% Confidence Interval)	45.6 (37.9 to 53.4)	35.7 (28.5 to 43.5)

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

Statistical Analysis Overview	Comparison Groups	Cetuximab Plus FOLFOX-4, FOLFOX-4 Alone
	Comments	Assuming a difference in rate of best confirmed response of at least 20% between the 2 treatments, ie an approximately 70% response rate under cetuximab plus FOLFOX-4 & 50% under FOLFOX-4 alone for the stratum with ECOG PS0–1 & 66% and 45% respectively for the ECOG PS2 stratum, the common OddsR over the strata was expected to be 2.33. A sample size of approximately 146/group was calculated as necessary to detect a significant overall response of at least 2.33 at level α=0.05 with a power of 90%

	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.064
	Comments	[Not specified]
	Method	Other [stratified Cochran-Mantel-Haenszel test]
	Comments	Stratified odds ratio and Cochran-Mantel-Haenszel (CMH) statistics were calculated considering the randomization strata.

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	1.516
	Confidence Interval	(2-Sided) 95% 0.975 to 2.335
	Estimation Comments	[Not specified]

2. Secondary Outcome Measure:

Measure Title	Best Overall Response Rate (Chinese V-Ki-ras2 Kirsten Rat Sarcoma Viral Oncogene Homolog (KRAS) Wild-Type Population)
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) as assessed by an IRC.
Time Frame	Evaluations were performed every 6 weeks until progression, reported between day of first patient randomised, 27 Jul 2005, until cut-off date 1 Mar 2007
Safety Issue?	No

Analysis Population Description

KRAS Wild-Type population

Reporting Groups

	Description
Cetuximab Plus FOLFOX-4	Cetuximab plus 5-Fluorouracil(5-FU)/Folinic acid (FA) and oxaliplatin. Cetuximab will always be administered first, followed by oxaliplatin at least 1 hour later. Following completion of the oxaliplatin infusion or simultaneously with oxaliplatin FA will be administered (at a dose of 200 mg/m^2, infused over 120 minutes, on day 1 and day 2, every two weeks) and then 5-FU (as a bolus of 400 mg/m^2/day intravenously (IV) over 2-4 minutes followed by 600 mg/m^2/day infused over 22-hour, on day 1 and day 2, every two weeks). Until progression or unacceptable toxicity develops. Safety population: includes all treated subjects.
FOLFOX-4 Alone	5-FU/FA and oxaliplatin. Oxaliplatin will always be administered first or simultaneously with FA (at a dose of 200 mg/m^2, infused over 120 minutes, on day 1 and day 2, every two weeks) and then 5-FU (as a bolus of 400 mg/m^2/day IV over 2-4 minutes followed by 600 mg/m^2/day infused over 22-hour, on day 1 and day 2, every two weeks). Until progression or unacceptable toxicity develops. Safety population: includes all treated subjects.

Measured Values

	Cetuximab Plus FOLFOX-4	FOLFOX-4 Alone
Number of Participants Analyzed	82	97
Best Overall Response Rate (Chinese V-Ki-ras2 Kirsten Rat Sarcoma Viral Oncogene Homolog (KRAS) Wild-Type Population) [units: percentage of participants] Number (95% Confidence Interval)	57.3 (45.9 to 68.2)	34.0 (24.7 to 44.3)

Statistical Analysis 1 for Best Overall Response Rate (Chinese V-Ki-ras2 Kirsten Rat Sarcoma Viral Oncogene Homolog (KRAS) Wild-Type Population)

Statistical Analysis Overview	Comparison Groups	Cetuximab Plus FOLFOX-4, FOLFOX-4 Alone
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0027
	Comments	[Not specified]
	Method	Other [stratified Cochran-Mantel-Haenszel test]
	Comments	Stratified odds ratio and Cochran-Mantel-Haenszel (CMH) statistics were calculated considering the randomization strata.

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	2.551
	Confidence Interval	(2-Sided) 95% 1.380 to 4.717
	Estimation Comments	[Not specified]

3. Secondary Outcome Measure:

Measure Title	Best Overall Response Rate (KRAS Mutant Population)
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) as assessed by an IRC.
Time Frame	Evaluations were performed every 6 weeks until progression, reported between day of first patient randomised, 27 Jul 2005, until cut-off date 1 Mar 2007
Safety Issue?	No

Analysis Population Description

KRAS Mutant population

Reporting Groups

	Description
Cetuximab Plus FOLFOX-4	Cetuximab plus 5-Fluorouracil(5-FU)/Folinic acid (FA) and oxaliplatin. Cetuximab will always be administered first, followed by oxaliplatin at least 1 hour later. Following completion of the oxaliplatin infusion or simultaneously with oxaliplatin FA will be administered (at a dose of 200 mg/m^2, infused over 120 minutes, on day 1 and day 2, every two weeks) and then 5-FU (as a bolus of 400 mg/m^2/day intravenously (IV) over 2-4 minutes followed by 600 mg/m^2/day infused over 22-hour, on day 1 and day 2, every two weeks). Until progression or unacceptable toxicity develops. Safety population: includes all treated subjects.
FOLFOX-4 Alone	5-FU/FA and oxaliplatin. Oxaliplatin will always be administered first or simultaneously with FA (at a dose of 200 mg/m^2, infused over 120 minutes, on day 1 and day 2, every two weeks) and then 5-FU (as a bolus of 400 mg/m^2/day IV over 2-4 minutes followed by 600 mg/m^2/day infused over 22-hour, on day 1 and day 2, every two weeks). Until progression or unacceptable toxicity develops. Safety population: includes all treated subjects.

Measured Values

	Cetuximab Plus FOLFOX-4	FOLFOX-4 Alone
Number of Participants Analyzed	77	59

	Cetuximab Plus FOLFOX-4	FOLFOX-4 Alone
Best Overall Response Rate (KRAS Mutant Population) [units: percentage of participants] Number (95% Confidence Interval)	33.8 (23.4 to 45.5)	52.5 (39.1 to 65.7)

Statistical Analysis 1 for Best Overall Response Rate (KRAS Mutant Population)

Statistical Analysis Overview	Comparison Groups	Cetuximab Plus FOLFOX-4, FOLFOX-4 Alone
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0290
	Comments	[Not specified]
	Method	Other [stratified Cochran-Mantel-Haenszel test]
	Comments	Stratified odds ratio and Cochran-Mantel-Haenszel (CMH) statistics were calculated considering the randomization strata.

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	0.459
	Confidence Interval	(2-Sided) 95% 0.228 to 0.924
	Estimation Comments	[Not specified]

4. Secondary Outcome Measure:

Measure Title	Progression-free Survival Time
Measure Description	Duration from randomization until radiological progression as assessed by an IRC (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, 27 Jul 2005, until cut-off date 01 Mar 2007

Safety Issue?	No

Analysis Population Description

Primary analysis on 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 FOLFOX-4	Cetuximab plus 5-Fluorouracil(5-FU)/Folinic acid (FA) and oxaliplatin. Cetuximab will always be administered first, followed by oxaliplatin at least 1 hour later. Following completion of the oxaliplatin infusion or simultaneously with oxaliplatin FA will be administered (at a dose of 200 mg/m^2, infused over 120 minutes, on day 1 and day 2, every two weeks) and then 5-FU (as a bolus of 400 mg/m^2/day intravenously (IV) over 2-4 minutes followed by 600 mg/m^2/day infused over 22-hour, on day 1 and day 2, every two weeks). Until progression or unacceptable toxicity develops. Safety population: includes all treated subjects.
FOLFOX-4 Alone	5-FU/FA and oxaliplatin. Oxaliplatin will always be administered first or simultaneously with FA (at a dose of 200 mg/m^2, infused over 120 minutes, on day 1 and day 2, every two weeks) and then 5-FU (as a bolus of 400 mg/m^2/day IV over 2-4 minutes followed by 600 mg/m^2/day infused over 22-hour, on day 1 and day 2, every two weeks). Until progression or unacceptable toxicity develops. Safety population: includes all treated subjects.

Measured Values

	Cetuximab Plus FOLFOX-4	FOLFOX-4 Alone
Number of Participants Analyzed	169	168
Progression-free Survival Time [units: months] Median (95% Confidence Interval)	7.2 (5.6 to 7.7)	7.2 (6.0 to 7.8)

Statistical Analysis 1 for Progression-free Survival Time

Statistical Analysis Overview	Comparison Groups	Cetuximab Plus FOLFOX-4, FOLFOX-4 Alone
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.6170
	Comments	[Not specified]

	Method	Other [Stratified Log Rank]
	Comments	Kaplan-Meier method 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	0.931
	Confidence Interval	(2-Sided) 95% 0.705 to 1.230
	Estimation Comments	[Not specified]

5. Secondary Outcome Measure:

Measure Title	Progression-free Survival Time (KRAS Wild-Type Population)
Measure Description	Duration from randomization until radiological progression as assessed by an IRC (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, 27 Jul 2005, until cut-off date 30 Nov 2008
Safety Issue?	No

Analysis Population Description
KRAS Wild-Type population

Reporting Groups

	Description
Cetuximab Plus FOLFOX-4	Cetuximab plus 5-Fluorouracil(5-FU)/Folinic acid (FA) and oxaliplatin. Cetuximab will always be administered first, followed by oxaliplatin at least 1 hour later. Following completion of the oxaliplatin infusion or simultaneously with oxaliplatin FA will be administered (at a dose of 200 mg/m^2, infused over 120 minutes, on day 1 and day 2, every two weeks) and then 5-FU (as a bolus of 400 mg/m^2/day intravenously (IV) over 2-4 minutes followed by 600 mg/m^2/day infused over 22-hour, on day 1 and day 2, every two weeks). Until progression or unacceptable toxicity develops. Safety population: includes all treated subjects.
FOLFOX-4 Alone	5-FU/FA and oxaliplatin. Oxaliplatin will always be administered first or simultaneously with FA (at a dose of 200 mg/m^2, infused over 120 minutes, on day 1 and day 2, every two weeks) and then 5-FU (as a bolus of 400 mg/m^2/day IV over 2-4 minutes followed by 600 mg/m^2/day infused over 22-hour, on day 1 and day 2, every two weeks). Until progression or unacceptable toxicity develops. Safety population: includes all treated subjects.

Measured Values

	Cetuximab Plus FOLFOX-4	FOLFOX-4 Alone
Number of Participants Analyzed	82	97
Progression-free Survival Time (KRAS Wild-Type Population) [units: months] Median (95% Confidence Interval)	8.3 (7.2 to 12.0)	7.2 (5.6 to 7.4)

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

Statistical Analysis Overview	Comparison Groups	Cetuximab Plus FOLFOX-4, FOLFOX-4 Alone
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0064
	Comments	[Not specified]
	Method	Other [Stratified Log Rank]
	Comments	Kaplan-Meier method 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	0.567
	Confidence Interval	(2-Sided) 95% 0.375 to 0.856
	Estimation Comments	[Not specified]

6. Secondary Outcome Measure:

Measure Title	Progression-free Survival Time (KRAS Mutant Population)
Measure Description	Duration from randomization until radiological progression as assessed by an IRC (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, 27 Jul 2005, until cut-off date 30 Nov 2008
Safety Issue?	No

Analysis Population Description
KRAS Mutant population

Reporting Groups

	Description
Cetuximab Plus FOLFOX-4	Cetuximab plus 5-Fluorouracil(5-FU)/Folinic acid (FA) and oxaliplatin. Cetuximab will always be administered first, followed by oxaliplatin at least 1 hour later. Following completion of the oxaliplatin infusion or simultaneously with oxaliplatin FA will be administered (at a dose of 200 mg/m^2, infused over 120 minutes, on day 1 and day 2, every two weeks) and then 5-FU (as a bolus of 400 mg/m^2/day intravenously (IV) over 2-4 minutes followed by 600 mg/m^2/day infused over 22-hour, on day 1 and day 2, every two weeks). Until progression or unacceptable toxicity develops. Safety population: includes all treated subjects.
FOLFOX-4 Alone	5-FU/FA and oxaliplatin. Oxaliplatin will always be administered first or simultaneously with FA (at a dose of 200 mg/m^2, infused over 120 minutes, on day 1 and day 2, every two weeks) and then 5-FU (as a bolus of 400 mg/m^2/day IV over 2-4 minutes followed by 600 mg/m^2/day infused over 22-hour, on day 1 and day 2, every two weeks). Until progression or unacceptable toxicity develops. Safety population: includes all treated subjects.

Measured Values

	Cetuximab Plus FOLFOX-4	FOLFOX-4 Alone
Number of Participants Analyzed	77	59
Progression-free Survival Time (KRAS Mutant Population) [units: months] Median (95% Confidence Interval)	5.5 (4.0 to 7.3)	8.6 (6.5 to 9.4)

Statistical Analysis 1 for Progression-free Survival Time (KRAS Mutant Population)

Statistical Analysis Overview	Comparison Groups	Cetuximab Plus FOLFOX-4, FOLFOX-4 Alone
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0153
	Comments	[Not specified]
	Method	Other [Stratified Log Rank]
	Comments	Kaplan-Meier method 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	1.720
	Confidence Interval	(2-Sided) 95% 1.104 to 2.679
	Estimation Comments	[Not specified]

7. Secondary Outcome Measure:

Measure Title	Overall Survival Time
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, whatever is earlier.
Time Frame	Time from randomisation to death or last day known to be alive, reported between day of first patient randomised, 27 Jul 2005, until cut-off date 30 Nov 2008
Safety Issue?	No

Analysis Population Description

Primary analysis on 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 FOLFOX-4	Cetuximab plus 5-Fluorouracil(5-FU)/Folinic acid (FA) and oxaliplatin. Cetuximab will always be administered first, followed by oxaliplatin at least 1 hour later. Following completion of the oxaliplatin infusion or simultaneously with oxaliplatin FA will be administered (at a dose of 200 mg/m^2, infused over 120 minutes, on day 1 and day 2, every two weeks) and then 5-FU (as a bolus of 400 mg/m^2/day intravenously (IV) over 2-4 minutes followed by 600 mg/m^2/day infused over 22-hour, on day 1 and day 2, every two weeks). Until progression or unacceptable toxicity develops. Safety population: includes all treated subjects.

	Description
FOLFOX-4 Alone	5-FU/FA and oxaliplatin. Oxaliplatin will always be administered first or simultaneously with FA (at a dose of 200 mg/m^2, infused over 120 minutes, on day 1 and day 2, every two weeks) and then 5-FU (as a bolus of 400 mg/m^2/day IV over 2-4 minutes followed by 600 mg/m^2/day infused over 22-hour, on day 1 and day 2, every two weeks). Until progression or unacceptable toxicity develops. Safety population: includes all treated subjects.

Measured Values

	Cetuximab Plus FOLFOX-4	FOLFOX-4 Alone
Number of Participants Analyzed	169	168
Overall Survival Time [units: months] Median (95% Confidence Interval)	18.3 (14.8 to 20.4)	18.0 (16.7 to 21.8)

Statistical Analysis 1 for Overall Survival Time

Statistical Analysis Overview	Comparison Groups	Cetuximab Plus FOLFOX-4, FOLFOX-4 Alone
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.9050
	Comments	[Not specified]
	Method	Other [Stratified log rank]
	Comments	Kaplan-Meier method 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	1.015
	Confidence Interval	(2-Sided) 95% 0.791 to 1.303
	Estimation Comments	[Not specified]

8. 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, whatever is earlier.
Time Frame	Time from randomisation to death or last day known to be alive, reported between day of first patient randomised, 27 Jul 2005, until cut-off date 30 November 2008
Safety Issue?	No

Analysis Population Description

KRAS Wild-Type population

Reporting Groups

	Description
Cetuximab Plus FOLFOX-4	Cetuximab plus 5-Fluorouracil(5-FU)/Folinic acid (FA) and oxaliplatin. Cetuximab will always be administered first, followed by oxaliplatin at least 1 hour later. Following completion of the oxaliplatin infusion or simultaneously with oxaliplatin FA will be administered (at a dose of 200 mg/m^2, infused over 120 minutes, on day 1 and day 2, every two weeks) and then 5-FU (as a bolus of 400 mg/m^2/day intravenously (IV) over 2-4 minutes followed by 600 mg/m^2/day infused over 22-hour, on day 1 and day 2, every two weeks). Until progression or unacceptable toxicity develops. Safety population: includes all treated subjects.
FOLFOX-4 Alone	5-FU/FA and oxaliplatin. Oxaliplatin will always be administered first or simultaneously with FA (at a dose of 200 mg/m^2, infused over 120 minutes, on day 1 and day 2, every two weeks) and then 5-FU (as a bolus of 400 mg/m^2/day IV over 2-4 minutes followed by 600 mg/m^2/day infused over 22-hour, on day 1 and day 2, every two weeks). Until progression or unacceptable toxicity develops. Safety population: includes all treated subjects.

Measured Values

	Cetuximab Plus FOLFOX-4	FOLFOX-4 Alone
Number of Participants Analyzed	82	97
Overall Survival Time (KRAS Wild-Type Population) [units: months] Median (95% Confidence Interval)	22.8 (19.3 to 25.9)	18.5 (16.4 to 22.6)

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

Statistical Analysis Overview	Comparison Groups	Cetuximab Plus FOLFOX-4, FOLFOX-4 Alone
	Comments	[Not specified]

	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.3854
	Comments	[Not specified]
	Method	Other [Stratified log rank]
	Comments	Kaplan-Meier method 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	0.855
	Confidence Interval	(2-Sided) 95% 0.599 to 1.219
	Estimation Comments	[Not specified]

9. 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, whatever is earlier.
Time Frame	Time from randomisation to death or last day known to be alive, reported between day of first patient randomised, 27 Jul 2005, until cut-off date 30 November 2008
Safety Issue?	No

Analysis Population Description

KRAS Mutant population

Reporting Groups

	Description
Cetuximab Plus FOLFOX-4	Cetuximab plus 5-Fluorouracil(5-FU)/Folinic acid (FA) and oxaliplatin. Cetuximab will always be administered first, followed by oxaliplatin at least 1 hour later. Following completion of the oxaliplatin infusion or simultaneously with oxaliplatin FA will be administered (at a dose of 200 mg/m^2, infused over 120 minutes, on day 1 and day 2, every two weeks) and then 5-FU (as a bolus of 400 mg/m^2/day intravenously (IV) over 2-4 minutes followed by 600 mg/m^2/day infused over 22-hour, on day 1 and day 2, every two weeks). Until progression or unacceptable toxicity develops. Safety population: includes all treated subjects.

	Description
FOLFOX-4 Alone	5-FU/FA and oxaliplatin. Oxaliplatin will always be administered first or simultaneously with FA (at a dose of 200 mg/m^2, infused over 120 minutes, on day 1 and day 2, every two weeks) and then 5-FU (as a bolus of 400 mg/m^2/day IV over 2-4 minutes followed by 600 mg/m^2/day infused over 22-hour, on day 1 and day 2, every two weeks). Until progression or unacceptable toxicity develops. Safety population: includes all treated subjects.

Measured Values

	Cetuximab Plus FOLFOX-4	FOLFOX-4 Alone
Number of Participants Analyzed	77	59
Overall Survival Time (KRAS Mutant Population) [units: months] Median (95% Confidence Interval)	13.4 (10.5 to 17.7)	17.5 (14.7 to 24.8)

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

Statistical Analysis Overview	Comparison Groups	Cetuximab Plus FOLFOX-4, FOLFOX-4 Alone
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.2004
	Comments	[Not specified]
	Method	Other [Stratified log rank]
	Comments	Kaplan-Meier method 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	1.290
	Confidence Interval	(2-Sided) 95% 0.873 to 1.906
	Estimation Comments	[Not specified]

10. Secondary Outcome Measure:

Measure Title	Participants With No Residual Tumor After Metastatic Surgery
Measure Description	No residual tumor after on-study surgery for metastases.
Time Frame	Time from first dose up to 30 days after the last dose of study treatment, reported between day of first patient randomised, 27 Jul 2005, until cut-off date 30 November 2008
Safety Issue?	No

Analysis Population Description

Primary analysis on 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 FOLFOX-4	Cetuximab plus 5-Fluorouracil(5-FU)/Folinic acid (FA) and oxaliplatin. Cetuximab will always be administered first, followed by oxaliplatin at least 1 hour later. Following completion of the oxaliplatin infusion or simultaneously with oxaliplatin FA will be administered (at a dose of 200 mg/m^2, infused over 120 minutes, on day 1 and day 2, every two weeks) and then 5-FU (as a bolus of 400 mg/m^2/day intravenously (IV) over 2-4 minutes followed by 600 mg/m^2/day infused over 22-hour, on day 1 and day 2, every two weeks). Until progression or unacceptable toxicity develops. Safety population: includes all treated subjects.
FOLFOX-4 Alone	5-FU/FA and oxaliplatin. Oxaliplatin will always be administered first or simultaneously with FA (at a dose of 200 mg/m^2, infused over 120 minutes, on day 1 and day 2, every two weeks) and then 5-FU (as a bolus of 400 mg/m^2/day IV over 2-4 minutes followed by 600 mg/m^2/day infused over 22-hour, on day 1 and day 2, every two weeks). Until progression or unacceptable toxicity develops. Safety population: includes all treated subjects.

Measured Values

	Cetuximab Plus FOLFOX-4	FOLFOX-4 Alone
Number of Participants Analyzed	169	168
Participants With No Residual Tumor After Metastatic Surgery [units: participants]	8	4

11. Secondary Outcome Measure:

Measure Title	Disease Control Rate (Cut Off Date 4 August 2006)

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 as assessed by IRC (based on modified WHO criteria).
Time Frame	Evaluations were performed every 6 weeks until progression, reported between day of first patient randomised, 27 Jul 2005, until cut-off date 4 August 2006
Safety Issue?	No

Analysis Population Description

Primary analysis on 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 FOLFOX-4	Cetuximab plus 5-Fluorouracil(5-FU)/Folinic acid (FA) and oxaliplatin. Cetuximab will always be administered first, followed by oxaliplatin at least 1 hour later. Following completion of the oxaliplatin infusion or simultaneously with oxaliplatin FA will be administered (at a dose of 200 mg/m^2, infused over 120 minutes, on day 1 and day 2, every two weeks) and then 5-FU (as a bolus of 400 mg/m^2/day intravenously (IV) over 2-4 minutes followed by 600 mg/m^2/day infused over 22-hour, on day 1 and day 2, every two weeks). Until progression or unacceptable toxicity develops. Safety population: includes all treated subjects.
FOLFOX-4 Alone	5-FU/FA and oxaliplatin. Oxaliplatin will always be administered first or simultaneously with FA (at a dose of 200 mg/m^2, infused over 120 minutes, on day 1 and day 2, every two weeks) and then 5-FU (as a bolus of 400 mg/m^2/day IV over 2-4 minutes followed by 600 mg/m^2/day infused over 22-hour, on day 1 and day 2, every two weeks). Until progression or unacceptable toxicity develops. Safety population: includes all treated subjects.

Measured Values

	Cetuximab Plus FOLFOX-4	FOLFOX-4 Alone
Number of Participants Analyzed	169	168
Disease Control Rate (Cut Off Date 4 August 2006) [units: percentage of participants] Number (95% Confidence Interval)	85.2 (78.9 to 90.2)	81.0 (74.2 to 86.6)

12. Secondary Outcome Measure:

Measure Title	Duration of Response

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, 27 Jul 2005, until cut-off date 01 Mar 2007
Safety Issue?	No

Analysis Population Description

Primary analysis on 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 FOLFOX-4	Cetuximab plus 5-Fluorouracil(5-FU)/Folinic acid (FA) and oxaliplatin. Cetuximab will always be administered first, followed by oxaliplatin at least 1 hour later. Following completion of the oxaliplatin infusion or simultaneously with oxaliplatin FA will be administered (at a dose of 200 mg/m^2, infused over 120 minutes, on day 1 and day 2, every two weeks) and then 5-FU (as a bolus of 400 mg/m^2/day intravenously (IV) over 2-4 minutes followed by 600 mg/m^2/day infused over 22-hour, on day 1 and day 2, every two weeks). Until progression or unacceptable toxicity develops. Safety population: includes all treated subjects.
FOLFOX-4 Alone	5-FU/FA and oxaliplatin. Oxaliplatin will always be administered first or simultaneously with FA (at a dose of 200 mg/m^2, infused over 120 minutes, on day 1 and day 2, every two weeks) and then 5-FU (as a bolus of 400 mg/m^2/day IV over 2-4 minutes followed by 600 mg/m^2/day infused over 22-hour, on day 1 and day 2, every two weeks). Until progression or unacceptable toxicity develops. Safety population: includes all treated subjects.

Measured Values

	Cetuximab Plus FOLFOX-4	FOLFOX-4 Alone
Number of Participants Analyzed	169	168
Duration of Response [units: months] Median (95% Confidence Interval)	9.0 (5.9 to 11.1)	5.7 (5.4 to 7.7)

13. 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 after last dose of study treatment, reported between day of first patient dose of study treatment, 27 Jul 2005, until cut-off date 30 Nov 2008
Safety Issue?	Yes

Analysis Population Description
Safety Population

Reporting Groups

	Description
Cetuximab Plus FOLFOX-4	Cetuximab plus 5-Fluorouracil(5-FU)/Folinic acid (FA) and oxaliplatin. Cetuximab will always be administered first, followed by oxaliplatin at least 1 hour later. Following completion of the oxaliplatin infusion or simultaneously with oxaliplatin FA will be administered (at a dose of 200 mg/m^2, infused over 120 minutes, on day 1 and day 2, every two weeks) and then 5-FU (as a bolus of 400 mg/m^2/day intravenously (IV) over 2-4 minutes followed by 600 mg/m^2/day infused over 22-hour, on day 1 and day 2, every two weeks). Until progression or unacceptable toxicity develops. Safety population: includes all treated subjects.
FOLFOX-4 Alone	5-FU/FA and oxaliplatin. Oxaliplatin will always be administered first or simultaneously with FA (at a dose of 200 mg/m^2, infused over 120 minutes, on day 1 and day 2, every two weeks) and then 5-FU (as a bolus of 400 mg/m^2/day IV over 2-4 minutes followed by 600 mg/m^2/day infused over 22-hour, on day 1 and day 2, every two weeks). Until progression or unacceptable toxicity develops. Safety population: includes all treated subjects.

Measured Values

	Cetuximab Plus FOLFOX-4	FOLFOX-4 Alone
Number of Participants Analyzed	170	168
Safety - Number of Patients Experiencing Any Adverse Event [units: participants]	170	165

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 FOLFOX-4	Cetuximab plus 5-Fluorouracil(5-FU)/Folinic acid (FA) and oxaliplatin. Cetuximab will always be administered first, followed by oxaliplatin at least 1 hour later. Following completion of the oxaliplatin infusion or simultaneously with oxaliplatin FA will be administered (at a dose of 200 mg/m^2, infused over 120 minutes, on day 1 and day 2, every two weeks) and then 5-FU (as a bolus of 400 mg/m^2/day intravenously (IV) over 2-4 minutes followed by 600 mg/m^2/day infused over 22-hour, on day 1 and day 2, every two weeks). Until progression or unacceptable toxicity develops. Safety population: includes all treated subjects.
FOLFOX-4 Alone	5-FU/FA and oxaliplatin. Oxaliplatin will always be administered first or simultaneously with FA (at a dose of 200 mg/m^2, infused over 120 minutes, on day 1 and day 2, every two weeks) and then 5-FU (as a bolus of 400 mg/m^2/day IV over 2-4 minutes followed by 600 mg/m^2/day infused over 22-hour, on day 1 and day 2, every two weeks). Until progression or unacceptable toxicity develops. Safety population: includes all treated subjects.

Serious Adverse Events

	Cetuximab Plus FOLFOX-4	FOLFOX-4 Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Total	61/170 (35.88%)	43/168 (25.6%)
Blood and lymphatic system disorders		
ANAEMIA [A] †	0/170 (0%)	1/168 (0.6%)
FEBRILE BONE MARROW APLASIA [A] †	0/170 (0%)	1/168 (0.6%)
FEBRILE NEUTROPENIA [A] †	4/170 (2.35%)	3/168 (1.79%)
LEUKOPENIA [A] †	3/170 (1.76%)	2/168 (1.19%)
NEUTROPENIA [A] †	4/170 (2.35%)	5/168 (2.98%)
THROMBOCYTOPENIA [A] †	0/170 (0%)	1/168 (0.6%)
Cardiac disorders		
ACUTE MYOCARDIAL INFARCTION [A] †	1/170 (0.59%)	0/168 (0%)
ARRHYTHMIA SUPRAVENTRICULAR [A] †	2/170 (1.18%)	0/168 (0%)
ATRIAL FIBRILLATION [A] †	1/170 (0.59%)	0/168 (0%)
CARDIAC FAILURE [A] †	1/170 (0.59%)	0/168 (0%)
CARDIO-RESPIRATORY ARREST [A] †	2/170 (1.18%)	0/168 (0%)

	Cetuximab Plus FOLFOX-4	FOLFOX-4 Alone
	Affected/At Risk (%)	Affected/At Risk (%)
LEFT VENTRICULAR DYSFUNCTION [A] †	1/170 (0.59%)	0/168 (0%)
Ear and labyrinth disorders		
VERTIGO [A] †	1/170 (0.59%)	0/168 (0%)
Eye disorders		
CONJUNCTIVITIS [A] †	1/170 (0.59%)	0/168 (0%)
Gastrointestinal disorders		
ABDOMINAL PAIN [A] †	2/170 (1.18%)	1/168 (0.6%)
ASCITES [A] †	2/170 (1.18%)	0/168 (0%)
COLITIS [A] †	1/170 (0.59%)	0/168 (0%)
CONSTIPATION [A] †	2/170 (1.18%)	0/168 (0%)
DIARRHOEA [A] †	2/170 (1.18%)	2/168 (1.19%)
GASTROINTESTINAL PERFORATION [A] †	0/170 (0%)	1/168 (0.6%)
HAEMATEMESIS [A] †	0/170 (0%)	1/168 (0.6%)
ILEUS [A] †	4/170 (2.35%)	1/168 (0.6%)
INTESTINAL OBSTRUCTION [A] †	3/170 (1.76%)	0/168 (0%)
LARGE INTESTINAL OBSTRUCTION [A] †	1/170 (0.59%)	0/168 (0%)
NAUSEA [A] †	0/170 (0%)	1/168 (0.6%)
PANCREATITIS [A] †	1/170 (0.59%)	0/168 (0%)
PERITONITIS [A] †	0/170 (0%)	1/168 (0.6%)
RECTAL STENOSIS [A] †	0/170 (0%)	1/168 (0.6%)
SUBILEUS [A] †	0/170 (0%)	1/168 (0.6%)
VOMITING [A] †	2/170 (1.18%)	4/168 (2.38%)
General disorders		

	Cetuximab Plus FOLFOX-4	FOLFOX-4 Alone
	Affected/At Risk (%)	Affected/At Risk (%)
ASTHENIA [A] †	3/170 (1.76%)	1/168 (0.6%)
CHEST PAIN [A] †	1/170 (0.59%)	0/168 (0%)
FATIGUE [A] †	1/170 (0.59%)	1/168 (0.6%)
GENERAL PHYSICAL HEALTH DETERIORATION [A] †	0/170 (0%)	1/168 (0.6%)
INJECTION SITE REACTION [A] †	1/170 (0.59%)	0/168 (0%)
MASS [A] †	1/170 (0.59%)	0/168 (0%)
MUCOSAL INFLAMMATION [A] †	1/170 (0.59%)	0/168 (0%)
OBSTRUCTION [A] †	0/170 (0%)	1/168 (0.6%)
PYREXIA [A] †	4/170 (2.35%)	4/168 (2.38%)
Hepatobiliary disorders		
BILE DUCT STONE [A] †	0/170 (0%)	1/168 (0.6%)
CHOLANGITIS [A] †	1/170 (0.59%)	0/168 (0%)
HEPATIC FAILURE [A] †	1/170 (0.59%)	0/168 (0%)
HEPATORENAL SYNDROME [A] †	1/170 (0.59%)	0/168 (0%)
HYPERBILIRUBINAEMIA [A] †	2/170 (1.18%)	0/168 (0%)
JAUNDICE [A] †	1/170 (0.59%)	0/168 (0%)
Immune system disorders		
HYPERSENSITIVITY [A] †	5/170 (2.94%)	2/168 (1.19%)
Infections and infestations		
ABSCESS NECK [A] †	0/170 (0%)	1/168 (0.6%)
BRONCHITIS [A] †	0/170 (0%)	1/168 (0.6%)
CATHETER RELATED INFECTION [A] †	0/170 (0%)	1/168 (0.6%)

	Cetuximab Plus FOLFOX-4	FOLFOX-4 Alone
	Affected/At Risk (%)	Affected/At Risk (%)
CENTRAL LINE INFECTION [A] †	0/170 (0%)	1/168 (0.6%)
ERYSIPELAS [A] †	2/170 (1.18%)	0/168 (0%)
FEBRILE INFECTION [A] †	1/170 (0.59%)	0/168 (0%)
INFECTION [A] †	2/170 (1.18%)	1/168 (0.6%)
KIDNEY INFECTION [A] †	0/170 (0%)	1/168 (0.6%)
LUNG ABSCESS [A] †	1/170 (0.59%)	0/168 (0%)
PERITONITIS BACTERIAL [A] †	1/170 (0.59%)	0/168 (0%)
PNEUMONIA [A] †	3/170 (1.76%)	3/168 (1.79%)
PULMONARY TUBERCULOSIS [A] †	1/170 (0.59%)	0/168 (0%)
PYELONEPHRITIS ACUTE [A] †	0/170 (0%)	1/168 (0.6%)
SEPSIS [A] †	1/170 (0.59%)	0/168 (0%)
STAPHYLOCOCCAL SEPSIS [A] †	1/170 (0.59%)	0/168 (0%)
TUBERCULOSIS [A] †	1/170 (0.59%)	0/168 (0%)
URINARY TRACT INFECTION [A] †	0/170 (0%)	1/168 (0.6%)
Injury, poisoning and procedural complications		
FALL [A] †	1/170 (0.59%)	0/168 (0%)
HUMERUS FRACTURE [A] †	1/170 (0.59%)	0/168 (0%)
INCISIONAL HERNIA [A] †	1/170 (0.59%)	0/168 (0%)
WOUND DEHISCENCE [A] †	1/170 (0.59%)	0/168 (0%)
Metabolism and nutrition disorders		
ANOREXIA [A] †	3/170 (1.76%)	0/168 (0%)
DEHYDRATION [A] †	2/170 (1.18%)	1/168 (0.6%)

	Cetuximab Plus FOLFOX-4	FOLFOX-4 Alone
	Affected/At Risk (%)	Affected/At Risk (%)
DIABETES MELLITUS INADEQUATE CONTROL [A] †	1/170 (0.59%)	0/168 (0%)
HYPERGLYCAEMIA [A] †	1/170 (0.59%)	0/168 (0%)
HYPOKALAEMIA [A] †	1/170 (0.59%)	0/168 (0%)
Nervous system disorders		
DEPRESSED LEVEL OF CONSCIOUSNESS [A] †	2/170 (1.18%)	0/168 (0%)
DIZZINESS [A] †	0/170 (0%)	1/168 (0.6%)
EPILEPSY [A] †	0/170 (0%)	1/168 (0.6%)
PERIPHERAL SENSORY NEUROPATHY [A] †	1/170 (0.59%)	0/168 (0%)
SYNCOPE [A] †	1/170 (0.59%)	0/168 (0%)
Psychiatric disorders		
ALCOHOLIC PSYCHOSIS [A] †	0/170 (0%)	1/168 (0.6%)
Renal and urinary disorders		
RENAL FAILURE [A] †	1/170 (0.59%)	0/168 (0%)
URINARY RETENTION [A] †	0/170 (0%)	1/168 (0.6%)
Respiratory, thoracic and mediastinal disorders		
DYSPNOEA [A] †	1/170 (0.59%)	0/168 (0%)
MEDIASTINAL HAEMATOMA [A] †	1/170 (0.59%)	0/168 (0%)
PULMONARY EMBOLISM [A] †	5/170 (2.94%)	2/168 (1.19%)
TACHYPNOEA [A] †	1/170 (0.59%)	0/168 (0%)
Surgical and medical procedures		
ILEOCOLOSTOMY [A] †	0/170 (0%)	1/168 (0.6%)

	Cetuximab Plus FOLFOX-4	FOLFOX-4 Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Vascular disorders		
AXILLARY VEIN THROMBOSIS [A] †	1/170 (0.59%)	0/168 (0%)
CIRCULATORY COLLAPSE [A] †	0/170 (0%)	1/168 (0.6%)
EMBOLISM [A] †	0/170 (0%)	1/168 (0.6%)
HYPERTENSION [A] †	2/170 (1.18%)	0/168 (0%)
HYPOTENSION [A] †	1/170 (0.59%)	0/168 (0%)
INTERMITTENT CLAUDICATION [A] †	1/170 (0.59%)	0/168 (0%)
PERIPHERAL ARTERIAL OCCLUSIVE DISEASE [A] †	1/170 (0.59%)	0/168 (0%)
THROMBOPHLEBITIS [A] †	0/170 (0%)	1/168 (0.6%)
VENOUS THROMBOSIS [A] †	1/170 (0.59%)	0/168 (0%)

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

Other Adverse Events

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

	Cetuximab Plus FOLFOX-4	FOLFOX-4 Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Total	170/170 (100%)	165/168 (98.21%)
Blood and lymphatic system disorders		
ANAEMIA [A] †	44/170 (25.88%)	41/168 (24.4%)
LEUKOPENIA [A] †	49/170 (28.82%)	43/168 (25.6%)
NEUTROPENIA [A] †	77/170 (45.29%)	84/168 (50%)
THROMBOCYTOPENIA [A] †	45/170 (26.47%)	69/168 (41.07%)
Ear and labyrinth disorders		

	Cetuximab Plus FOLFOX-4	FOLFOX-4 Alone
	Affected/At Risk (%)	Affected/At Risk (%)
VERTIGO [A] †	9/170 (5.29%)	7/168 (4.17%)
Eye disorders		
CONJUNCTIVITIS [A] †	23/170 (13.53%)	8/168 (4.76%)
Gastrointestinal disorders		
ABDOMINAL PAIN [A] †	30/170 (17.65%)	29/168 (17.26%)
CONSTIPATION [A] †	32/170 (18.82%)	16/168 (9.52%)
DIARRHOEA [A] †	81/170 (47.65%)	68/168 (40.48%)
DYSPEPSIA [A] †	9/170 (5.29%)	9/168 (5.36%)
NAUSEA [A] †	69/170 (40.59%)	65/168 (38.69%)
STOMATITIS [A] †	33/170 (19.41%)	19/168 (11.31%)
VOMITING [A] †	48/170 (28.24%)	37/168 (22.02%)
General disorders		
ASTHENIA [A] †	32/170 (18.82%)	31/168 (18.45%)
FATIGUE [A] †	54/170 (31.76%)	43/168 (25.6%)
MUCOSAL INFLAMMATION [A] †	22/170 (12.94%)	8/168 (4.76%)
PYREXIA [A] †	39/170 (22.94%)	30/168 (17.86%)
Immune system disorders		
HYPERSENSITIVITY [A] †	13/170 (7.65%)	1/168 (0.6%)
Infections and infestations		
PARONYCHIA [A] †	20/170 (11.76%)	0/168 (0%)
Investigations		
WEIGHT DECREASED [A] †	26/170 (15.29%)	19/168 (11.31%)
Metabolism and nutrition disorders		

	Cetuximab Plus FOLFOX-4	FOLFOX-4 Alone
	Affected/At Risk (%)	Affected/At Risk (%)
ANOREXIA [A] †	34/170 (20%)	23/168 (13.69%)
HYPOCALCAEMIA [A] †	10/170 (5.88%)	0/168 (0%)
HYPOKALAEMIA [A] †	11/170 (6.47%)	5/168 (2.98%)
HYPOMAGNESAEMIA [A] †	16/170 (9.41%)	2/168 (1.19%)
Musculoskeletal and connective tissue disorders		
BACK PAIN [A] †	10/170 (5.88%)	8/168 (4.76%)
Nervous system disorders		
DIZZINESS [A] †	11/170 (6.47%)	3/168 (1.79%)
HEADACHE [A] †	11/170 (6.47%)	8/168 (4.76%)
NEUROPATHY [A] †	10/170 (5.88%)	16/168 (9.52%)
NEUROTOXICITY [A] †	12/170 (7.06%)	7/168 (4.17%)
PARAESTHESIA [A] †	19/170 (11.18%)	38/168 (22.62%)
PERIPHERAL SENSORY NEUROPATHY [A] †	46/170 (27.06%)	51/168 (30.36%)
POLYNEUROPATHY [A] †	9/170 (5.29%)	5/168 (2.98%)
Psychiatric disorders		
INSOMNIA [A] †	9/170 (5.29%)	6/168 (3.57%)
Respiratory, thoracic and mediastinal disorders		
COUGH [A] †	10/170 (5.88%)	7/168 (4.17%)
EPISTAXIS [A] †	15/170 (8.82%)	11/168 (6.55%)
Skin and subcutaneous tissue disorders		
ACNE [A] †	10/170 (5.88%)	0/168 (0%)
ALOPECIA [A] †	21/170 (12.35%)	17/168 (10.12%)

	Cetuximab Plus FOLFOX-4	FOLFOX-4 Alone
	Affected/At Risk (%)	Affected/At Risk (%)
DERMATITIS ACNEIFORM [A] †	38/170 (22.35%)	1/168 (0.6%)
DRY SKIN [A] †	28/170 (16.47%)	3/168 (1.79%)
EXFOLIATIVE RASH [A] †	12/170 (7.06%)	0/168 (0%)
NAIL DISORDER [A] †	11/170 (6.47%)	2/168 (1.19%)
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME [A] †	19/170 (11.18%)	7/168 (4.17%)
PRURITUS [A] †	15/170 (8.82%)	6/168 (3.57%)
RASH [A] †	90/170 (52.94%)	4/168 (2.38%)
SKIN FISSURES [A] †	17/170 (10%)	0/168 (0%)
SKIN TOXICITY [A] †	13/170 (7.65%)	0/168 (0%)
Vascular disorders		
HYPERTENSION [A] †	11/170 (6.47%)	8/168 (4.76%)

† 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 this entry in error. A replacement outcome has been created. The 'Safety' outcome refers to adverse events and these are shown in the 'Adverse Events' section.

More Information

Certain Agreements:

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

The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is more than 60 days but less than or equal to 180 days from the time submitted to the sponsor for review. The sponsor cannot require changes to the communication and cannot extend the embargo.

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