ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: 07/11/2014

ClinicalTrials.gov ID: NCT00122460

Study Identification

Unique Protocol ID:	EMR 62202-002
Brief Title:	Cetuximab (Erbitux) in Combination With Cisplatin or Carboplatin and 5-Fluorouracil in the First Line Treatment of Subjects With Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck (EXTREME)
Official Title:	Cetuximab in Combination With Cisplatin or Carboplatin and 5-Fluorouracil in the First Line Treatment of Subjects With Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck
Secondary IDs:	

Study Status

Record Verification:	July 2014
Overall Status:	Completed
Study Start:	December 2004
Primary Completion:	March 2007 [Actual]
Study Completion:	January 2011 [Actual]

Sponsor/Collaborators

Sponsor:	Merck KGaA
Responsible Party:	Sponsor
Collaborators:	

Oversight

FDA Regulated?:	Yes

Applicable Trial?:	Section 801 Clinical Trial? Yes Delayed Posting? No
IND/IDE Protocol?:	No
Review Board:	Approval Status: Approved Approval Number: 4/41/122 Board Name: Comité voor Medische Thiek Board Affiliation: EC UZ Antwerpen Phone: ++32 (0) 3 821 Email: Erika.Dries@uza.be
Data Monitoring?:	Yes
Plan to Share Data?:	
Oversight Authorities:	Belgium: Federal Agency for Medicines and Health Products, FAMHP

Study Description

Brief Summary:	The purpose of this trial is to investigate the efficacy of cetuximab in combination with chemotherapy in comparison to chemotherapy alone in patients with recurrent or metastatic head and neck cancer. Overall survival will be taken as the primary measure of efficacy.
Detailed Description:	

Conditions

Conditions:	Head and Neck Cancer
Keywords:	Head and Neck Cancer

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: Efficacy Study

Enrollment: 442 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Cetuximab Plus Chemotherapy	Drug: Cetuximab + Platinum (Cisplatin or Carboplatin) + 5Fluorouracil (5-FU) Subjects in will receive initial dose of 400 mg/m^2 cetuximab (over 2 hours) followed by weekly doses of 250 mg/m^2 (over 1 hour). All doses will be given by intravenous (IV) infusion. Subjects will receive either Cisplatin (100 mg/m^2 on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks or Carboplatin (Area under the curve (AUC) 5 IV on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks
Active Comparator: Chemotherapy alone	Drug: Platinum (Cisplatin or Carboplatin) + 5-FU All doses will be given by IV infusion. Subjects will receive either Cisplatin (100 mg/m^2 on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks or Carboplatin (AUC 5 IV on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age:

Gender: Both

Accepts Healthy Volunteers?: No

Criteria: Inclusion Criteria:

- Histologically or cytologically confirmed diagnosis of squamous cell carcinoma of the head and neck (SCCHN)
- Recurrent and/or metastatic SCCHN, not suitable for local therapy

Exclusion Criteria:

- Prior systemic chemotherapy, except if given as part of a multimodal treatment for locally advanced disease which was completed more than 6 months prior to study entry
- Surgery (excluding prior diagnostic biopsy), or irradiation within 4 weeks before study entry
- Nasopharyngeal carcinoma

Contacts/Locations

Study Officials: Medical Responsible
Study Director
Merck KGaA

Locations: Belgium
Research Site
Edegem, Belgium

Austria
Research Site
Wien, Austria

Research Site
Innsbruck, Austria

Belgium
Research Site
Bruxelles, Belgium

Research Site
Gent, Belgium

Switzerland
Research Site
Thun, Switzerland

Research Site
Zürich, Switzerland

Research Site
Geneva, Switzerland

Czech Republic
Research Site
Ceske Budejovice, Czech Republic

Research Site
Prague, Czech Republic

Germany
Research Site
Essen, Germany

Research Site
Hamburg, Germany

Research Site
Frankfurt on the Main, Germany

Research Site
Berlin, Germany

Research Site
Oldenburg, Germany

Research Site
Munich, Germany

Research Site
Stuttgart, Germany

Spain
Research Site
Barcelona, Spain

Research Site
Madrid, Spain

Research Site
L'Hospitalet de Llobregat, Spain

Research Site
Santander, Spain

Research Site
Malaga, Spain

Research Site
San Sebastian, Spain

Research Site
Sevilla, Spain

Research Site
Valencia, Spain

France
Research Site
Strasbourg, France

Research Site
Tours, France

Research Site
Montpellier, France

Research Site
Caen, France

Research Site
Lille, France

Research Site
Marseille, France

Research Site
Vandoeuvre les Nancy, France

Research Site
Limoges, France

Research Site
Nice, France

Research Site
Nantes-Saint Herblain, France

Research Site
Dijon, France

Research Site
Toulouse, France

Hungary
Research Site
Nyiregyhaza, Hungary

Research Site
Gyor, Hungary

Research Site
Budapest, Hungary

Research Site
Kecskemet, Hungary

Italy
Research Site
Genoa, Italy

Research Site
Naples, Italy

Research Site
Milan, Italy

Research Site
Monserrato, Italy

Research Site
Cuneo, Italy

Research Site
Rome, Italy

Netherlands
Research Site
Amsterdam, Netherlands

Research Site
Nijmegen, Netherlands

Portugal
Research Site
Lisbon, Portugal

Research Site
Porto, Portugal

Poland
Research Site
Warszawa, Poland

Research Site
Gdansk, Poland

Research Site
Krakow, Poland

Russian Federation
Research Site
Moscow, Russian Federation

Research Site
St. Petersburg, Russian Federation

Sweden
Research Site
Lind, Sweden

Research Site
Örebo, Sweden

Research Site
Umea, Sweden

Slovakia
Research Site
Kosice, Slovakia

Research Site
Bratislava, Slovakia

United Kingdom
Research Site
London, United Kingdom

Research Site
Edinburgh, United Kingdom

Research Site
Nottingham, United Kingdom

Research Site
Manchester, United Kingdom

Research Site
Chelmsford, United Kingdom

Ukraine
Research Site
Donetsk, Ukraine

Research Site
Kharkiv, Ukraine

Research Site
Sumy, Ukraine

Research Site
Kiev, Ukraine

References

Citations: [Study Results] Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, Erfan J, Zabolotnyy D, Kienzer HR, Cupissol D, Peyrade F, Benasso M, Vynnychenko I, De Raucourt D, Bokemeyer C, Schueler A, Amellal N, Hitt R. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med. 2008 Sep 11;359(11):1116-27. doi: 10.1056/NEJMoa0802656. PubMed 18784101

[Study Results] Mesía R, Rivera F, Kawecki A, Rottey S, Hitt R, Kienzer H, Cupissol D, De Raucourt D, Benasso M, Koralewski P, Delord JP, Bokemeyer C, Curran D, Gross A, Vermorken JB. Quality of life of patients receiving platinum-based chemotherapy plus cetuximab first line for recurrent and/or metastatic squamous cell carcinoma of the head and neck. Ann Oncol. 2010 Oct;21(10):1967-73. doi: 10.1093/annonc/mdq077. Epub 2010 Mar 24. PubMed 20335368

Links:

Study Data/Documents:

Study Results

Participant Flow

Recruitment Details	First/last subject(informed consent): 14Dec 2004/28 Dec2005. Clinical cut-off: 12 Mar 2007. 80 centers in Europe: Austria (3), Belgium (5), Czech Republic (2), France (12),Germany (8), Hungary (4), Italy (5), Netherlands (4), Poland (5), Portugal (3), Russia (4), Slovakia (2), Spain (9), Sweden (3), Switzerland (3), UK (4), and Ukraine (4).
Pre-Assignment Details	477 subjects screened. 41 ineligible for treatment at end of screening (inclusion/exclusion criteria not fulfilled (30),death (3),consent withdrawal(3), symptomatic deterioration(2),non-compliance with timelines(1),refusal to continue study procedures (1), missing (1).436 eligible for treatment; however 6 of the ineligible patients were randomized

Reporting Groups

	Description
Cetuximab Plus Chemotherapy	Subjects in will receive initial dose of 400 mg/m^2 cetuximab (over 2 hours) followed by weekly doses of 250 mg/m^2 (over 1 hour). All doses will be given by intravenous (IV) infusion. Subjects will receive either Cisplatin (100 mg/m^2 on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks or Carboplatin (Area under the curve (AUC) 5 IV on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks.

	Description
Chemotherapy Alone	All doses will be given by IV infusion. Subjects will receive either Cisplatin (100 mg/m^2 on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks or Carboplatin (AUC 5 IV on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks.

Overall Study

	Cetuximab Plus Chemotherapy	Chemotherapy Alone
Started	222 [1]	220 [1]
Completed	215	219
Not Completed	7	1
investigational study phase ongoing	7	1

[1] Intention To Treat population, treatment group as randomized

Baseline Characteristics

Reporting Groups

	Description
Cetuximab Plus Chemotherapy	Subjects in will receive initial dose of 400 mg/m^2 cetuximab (over 2 hours) followed by weekly doses of 250 mg/m^2 (over 1 hour). All doses will be given by intravenous (IV) infusion. Subjects will receive either Cisplatin (100 mg/m^2 on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks or Carboplatin (Area under the curve (AUC) 5 IV on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks.
Chemotherapy Alone	All doses will be given by IV infusion. Subjects will receive either Cisplatin (100 mg/m^2 on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks or Carboplatin (AUC 5 IV on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks.

Baseline Measures

	Cetuximab Plus Chemotherapy	Chemotherapy Alone	Total
Number of Participants	222	220	442
Age, Categorical [units: participants]			
<=18 years	0	0	0
Between 18 and 65 years	183	182	365
>=65 years	39	38	77

	Cetuximab Plus Chemotherapy	Chemotherapy Alone	Total
Age, Continuous [units: years] Mean (Standard Deviation)	57.1 (8.0)	56.7 (8.7)	56.9 (8.3)
Gender, Male/Female [units: participants]			
Female	25	18	43
Male	197	202	399
Region of Enrollment [units: participants]			
Portugal	3	6	9
Slovakia	3	1	4
Spain	38	41	79
Ukraine	18	16	34
Austria	4	10	14
Russian Federation	9	7	16
United Kingdom	4	5	9
Switzerland	4	4	8
Italy	14	12	26
France	45	31	76
Czech Republic	4	5	9
Hungary	19	24	43
Belgium	14	16	30
Poland	18	18	36
Germany	18	14	32
Netherlands	4	6	10
Sweden	3	4	7

Outcome Measures

1. Primary 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, whatever is earlier.
Time Frame	time from randomization to death or last day known to be alive, reported between day of first patient randomised, 21 Dec 2004, until cut-off date 12 Mar 2007
Safety Issue?	No

Analysis Population Description

Primary analysis on Intent to Treat (ITT) population (allocation to treatment groups as randomized).

Analysis performed after the required number of 340 deaths had been reported (expected effect: 36% increase in median survival time, power = 80%, alpha=5% (two-sided)). The Clinical cut-off date was 12 Mar 2007.

Reporting Groups

	Description
Cetuximab Plus Chemotherapy	Subjects in will receive initial dose of 400 mg/m^2 cetuximab (over 2 hours) followed by weekly doses of 250 mg/m^2 (over 1 hour). All doses will be given by intravenous (IV) infusion. Subjects will receive either Cisplatin (100 mg/m^2 on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks or Carboplatin (Area under the curve (AUC) 5 IV on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks.
Chemotherapy Alone	All doses will be given by IV infusion. Subjects will receive either Cisplatin (100 mg/m^2 on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks or Carboplatin (AUC 5 IV on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks.

Measured Values

	Cetuximab Plus Chemotherapy	Chemotherapy Alone
Number of Participants Analyzed	222	220
Overall Survival Time (OS) [units: months] Median (95% Confidence Interval)	10.1 (8.6 to 11.2)	7.4 (6.4 to 8.3)

Statistical Analysis 1 for Overall Survival Time (OS)

Statistical Analysis Overview	Comparison Groups	Cetuximab Plus Chemotherapy, Chemotherapy Alone
	Comments	The primary analysis tested the equality of OS between treatment groups applying a 2-sided stratified log-rank test (α=5%), taking into account the strata used for randomization (previous chemotherapy (CTX) [no vs. yes] and Karnofsky Performance Status (KPS) [<80 vs. ≥80]). Median overall survival was estimated using the Kaplan-Meier method. The Hazard Ratio (HR) of cetuximab + CTX over CTX alone was calculated using the Cox proportional hazards model stratified by randomization strata.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.036
	Comments	[Not specified]
	Method	Other [Stratified Log Rank]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	0.797
	Confidence Interval	(2-Sided) 95% 0.644 to 0.986
	Estimation Comments	[Not specified]

2. Secondary Outcome Measure:

Measure Title	Progression-free Survival Time (PFS)
Measure Description	Duration from randomization until radiological progression according to investigator (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 randomization to disease progression, death or last tumor assessment, reported between day of first patient randomised, 21 Dec 2004, until cut-off date 12 Mar 2007
Safety Issue?	No

Analysis Population Description

Analysis on ITT population (allocation to treatment groups as randomized). Analysis performed at clinical cut off date, determined by primary endpoint.

Reporting Groups

	Description
Cetuximab Plus Chemotherapy	Subjects in will receive initial dose of 400 mg/m^2 cetuximab (over 2 hours) followed by weekly doses of 250 mg/m^2 (over 1 hour). All doses will be given by intravenous (IV) infusion. Subjects will receive either Cisplatin (100 mg/m^2 on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks or Carboplatin (Area under the curve (AUC) 5 IV on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks.
Chemotherapy Alone	All doses will be given by IV infusion. Subjects will receive either Cisplatin (100 mg/m^2 on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks or Carboplatin (AUC 5 IV on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks.

Measured Values

	Cetuximab Plus Chemotherapy	Chemotherapy Alone
Number of Participants Analyzed	222	220
Progression-free Survival Time (PFS) [units: months] Median (95% Confidence Interval)	5.6 (5.0 to 6.0)	3.3 (2.9 to 4.3)

Statistical Analysis 1 for Progression-free Survival Time (PFS)

Statistical Analysis Overview	Comparison Groups	Cetuximab Plus Chemotherapy, Chemotherapy Alone
	Comments	To test the equality of PFS between treatment groups, a two-sided stratified log-rank test (α=5%)was used, taking into account strata used for randomization (previous CTX [yes/no] and KPS [<80 vs. ≥80]). Median PFS time was estimated using the Kaplan-Meier method. The HR of cetuximab + CTX over CTX alone was calculated using the Cox proportional hazards model stratified by randomization strata.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Stratified Log Rank]

	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	0.538
	Confidence Interval	(2-Sided) 95% 0.431 to 0.672
	Estimation Comments	[Not specified]

3. Secondary Outcome Measure:

Measure Title	Best Overall Response
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 according to investigator (based on modified WHO criteria).
Time Frame	evaluations were performed every 6 weeks until progression, reported between day of first patient randomised, 21 Dec 2004, until cut-off date 12 Mar 2007
Safety Issue?	No

Analysis Population Description

Analysis on ITT population (allocation to treatment groups as randomized). Analysis performed at clinical cut off date, determined by primary endpoint.

Reporting Groups

	Description
Cetuximab Plus Chemotherapy	Subjects in will receive initial dose of 400 mg/m^2 cetuximab (over 2 hours) followed by weekly doses of 250 mg/m^2 (over 1 hour). All doses will be given by intravenous (IV) infusion. Subjects will receive either Cisplatin (100 mg/m^2 on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks or Carboplatin (Area under the curve (AUC) 5 IV on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks.
Chemotherapy Alone	All doses will be given by IV infusion. Subjects will receive either Cisplatin (100 mg/m^2 on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks or Carboplatin (AUC 5 IV on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks.

Measured Values

	Cetuximab Plus Chemotherapy	Chemotherapy Alone
Number of Participants Analyzed	222	220
Best Overall Response [units: percentage of participants] Number (95% Confidence Interval)	35.6 (29.3 to 42.3)	19.5 (14.5 to 25.4)

Statistical Analysis 1 for Best Overall Response

Statistical Analysis Overview	Comparison Groups	Cetuximab Plus Chemotherapy, Chemotherapy Alone
	Comments	A Cochran-Mantel-Haenszel (CMH) test was performed using the randomization strata previous CTX (no vs. yes) and KPS (<80 vs. ≥80). Treatment group comparisons were performed two-sided with α=5%.
	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	2.326
	Confidence Interval	(2-Sided) 95% 1.504 to 3.600
	Estimation Comments	[Not specified]

4. Secondary Outcome Measure:

Measure Title	Disease Control
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 according to investigator (based on modified WHO criteria).
Time Frame	evaluations were performed every 6 weeks until progression, reported between day of first patient randomised, 21 Dec 2004, until cut-off date 12 Mar 2007
Safety Issue?	No

Analysis Population Description

Analysis on ITT population (allocation to treatment groups as randomized). Analysis performed at clinical cut off date, determined by primary endpoint.

Reporting Groups

	Description
Cetuximab Plus Chemotherapy	Subjects in will receive initial dose of 400 mg/m^2 cetuximab (over 2 hours) followed by weekly doses of 250 mg/m^2 (over 1 hour). All doses will be given by intravenous (IV) infusion. Subjects will receive either Cisplatin (100 mg/m^2 on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks or Carboplatin (Area under the curve (AUC) 5 IV on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks.
Chemotherapy Alone	All doses will be given by IV infusion. Subjects will receive either Cisplatin (100 mg/m^2 on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks or Carboplatin (AUC 5 IV on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks.

Measured Values

	Cetuximab Plus Chemotherapy	Chemotherapy Alone
Number of Participants Analyzed	222	220
Disease Control [units: percentage of participants] Number (95% Confidence Interval)	81.1 (75.3 to 86.0)	60.0 (53.2 to 66.5)

Statistical Analysis 1 for Disease Control

Statistical Analysis Overview	Comparison Groups	Cetuximab Plus Chemotherapy, Chemotherapy Alone
	Comments	A Cochran-Mantel-Haenszel (CMH) test was performed using the randomization strata previous CTX (no vs. yes) and KPS (<80 vs. ≥80). Treatment group comparisons were performed two-sided with α=5%.
	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	2.881
	Confidence Interval	(2-Sided) 95%

		1.870 to 4.441
	Estimation Comments	[Not specified]

5. Secondary Outcome Measure:

Measure Title	Time to Treatment Failure
Measure Description	Time from randomization to date of the first occurrence of; progression, discontinuation of treatment due to progression or adverse event, start of new anticancer therapy, withdrawal of consent, or death (within 60 days of last tumor assessment). Patients without event are censored on the date of last tumor assessment.
Time Frame	Time from randomization to treatment failure or last tumor assessment, reported between day of first patient randomised, 21 Dec 2004, until cut-off date 12 Mar 2007
Safety Issue?	No

Analysis Population Description

Analysis on ITT population (allocation to treatment groups as randomized). Analysis performed at clinical cut off date, determined by primary endpoint.

Reporting Groups

	Description
Cetuximab Plus Chemotherapy	Subjects in will receive initial dose of 400 mg/m^2 cetuximab (over 2 hours) followed by weekly doses of 250 mg/m^2 (over 1 hour). All doses will be given by intravenous (IV) infusion. Subjects will receive either Cisplatin (100 mg/m^2 on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks or Carboplatin (Area under the curve (AUC) 5 IV on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks.
Chemotherapy Alone	All doses will be given by IV infusion. Subjects will receive either Cisplatin (100 mg/m^2 on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks or Carboplatin (AUC 5 IV on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks.

Measured Values

	Cetuximab Plus Chemotherapy	Chemotherapy Alone
Number of Participants Analyzed	222	220
Time to Treatment Failure [units: months] Median (95% Confidence Interval)	4.8 (4.0 to 5.6)	3.0 (2.8 to 3.4)

Statistical Analysis 1 for Time to Treatment Failure

Statistical Analysis Overview	Comparison Groups	Cetuximab Plus Chemotherapy, Chemotherapy Alone
	Comments	Treatment groups were compared applying a two-sided stratified log-rank test (α=5%), taking into account strata used for randomization (previous CTX [yes/no] and KPS [<80 vs. ≥80]). Median time to treatment failure was estimated using the Kaplan-Meier method. The HR of cetuximab + CTX over CTX alone was calculated using the Cox proportional hazards model stratified by randomization strata.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Stratified Log Rank]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	0.593
	Confidence Interval	(2-Sided) 95% 0.484 to 0.727
	Estimation Comments	[Not specified]

6. 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, 21 Dec 2004, until cut-off date 12 Mar 2007
Safety Issue?	No

Analysis Population Description

Analysis on ITT population (allocation to treatment groups as randomized). Analysis performed at clinical cut off date, determined by primary endpoint.

Reporting Groups

	Description
Cetuximab Plus Chemotherapy	Subjects in will receive initial dose of 400 mg/m^2 cetuximab (over 2 hours) followed by weekly doses of 250 mg/m^2 (over 1 hour). All doses will be given by intravenous (IV) infusion. Subjects will receive either Cisplatin (100 mg/m^2 on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks or Carboplatin (Area under the curve (AUC) 5 IV on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks.
Chemotherapy Alone	All doses will be given by IV infusion. Subjects will receive either Cisplatin (100 mg/m^2 on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks or Carboplatin (AUC 5 IV on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks.

Measured Values

	Cetuximab Plus Chemotherapy	Chemotherapy Alone
Number of Participants Analyzed	222	220
Duration of Response [units: months] Median (95% Confidence Interval)	5.6 (4.7 to 6.0)	4.7 (3.5 to 5.9)

Statistical Analysis 1 for Duration of Response

Statistical Analysis Overview	Comparison Groups	Cetuximab Plus Chemotherapy, Chemotherapy Alone
	Comments	To test the equality of duration of response between treatment groups, the two-sided stratified log-rank test (α=5%) was used taking strata used for randomization into account (previous CTX [no vs. yes] and KPS [<80 vs. ≥80]). Median duration of response was estimated using the Kaplan-Meier method. The HR of cetuximab + CTX over CTX alone was calculated using the Cox proportional hazards model stratified by randomization strata.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.21
	Comments	[Not specified]
	Method	Other [Stratified Log Rank]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	0.762
	Confidence Interval	(2-Sided) 95% 0.497 to 1.168
	Estimation Comments	[Not specified]

7. 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, day 1 of cycle 3, first 6-weekly evaluation following completion of chemotherapy, 6 & 12 months after randomization, reported between day of first patient randomised, 21 Dec 2004,until cut-off date, 12 Mar 2007
Safety Issue?	No

Analysis Population Description

Of 361 ITT subjects from countries with EORTC QLQ-C30 available, 291 completed ≥1 evaluable questionnaire. Only time points where ≥ 20% of patients completing a baseline questionnaire remained in the population were analysed. Numbers at each timepoint were (cetuximab+chemotherapy/chemotherapy alone): Baseline: 121/106; Cycle3:87/67; Month6:48/22

Reporting Groups

	Description
Cetuximab Plus Chemotherapy	Subjects in will receive initial dose of 400 mg/m^2 cetuximab (over 2 hours) followed by weekly doses of 250 mg/m^2 (over 1 hour). All doses will be given by intravenous (IV) infusion. Subjects will receive either Cisplatin (100 mg/m^2 on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks or Carboplatin (Area under the curve (AUC) 5 IV on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks.
Chemotherapy Alone	All doses will be given by IV infusion. Subjects will receive either Cisplatin (100 mg/m^2 on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks or Carboplatin (AUC 5 IV on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks.

Measured Values

	Cetuximab Plus Chemotherapy	Chemotherapy Alone
Number of Participants Analyzed	152	139

	Cetuximab Plus Chemotherapy	Chemotherapy Alone
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	50.74 (3.519)	45.15 (3.745)
At cycle 3	52.68 (3.724)	45.48 (4.153)
Month 6	55.30 (4.282)	42.49 (5.959)

8. 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 social functioning.
Time Frame	at baseline, day 1 of cycle 3, first 6-weekly evaluation following completion of chemotherapy, 6 & 12 months after randomization, reported between day of first patient randomised, 21 Dec 2004,until cut-off date, 12 Mar 2007
Safety Issue?	No

Analysis Population Description

Of 361 ITT subjects from countries with EORTC QLQ-C30 available, 291 completed ≥1 evaluable questionnaire. Only time points where ≥ 20% of patients completing a baseline questionnaire remained in the population were analysed. Numbers at each timepoint were (cetuximab +chemotherapy/chemotherapy alone): Baseline:123/109; Cycle3:87/69; Month6:48/23

Reporting Groups

	Description
Cetuximab Plus Chemotherapy	Subjects in will receive initial dose of 400 mg/m^2 cetuximab (over 2 hours) followed by weekly doses of 250 mg/m^2 (over 1 hour). All doses will be given by intravenous (IV) infusion. Subjects will receive either Cisplatin (100 mg/m^2 on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks or Carboplatin (Area under the curve (AUC) 5 IV on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks.
Chemotherapy Alone	All doses will be given by IV infusion. Subjects will receive either Cisplatin (100 mg/m^2 on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks or Carboplatin (AUC 5 IV on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks.

Measured Values

	Cetuximab Plus Chemotherapy	Chemotherapy Alone
Number of Participants Analyzed	152	139
Quality of Life Assessment (EORTC QLQ-C30) Social Functioning [units: scores on a scale] Least Squares Mean (Standard Error)		
At baseline	62.14 (4.459)	62.05 (4.730)
At cycle 3	64.64 (4.663)	60.67 (5.176)
Month 6	61.27 (5.347)	65.72 (7.122)

9. 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 dose of study treatment, 22 Dec 2004, until cut-off date 12 Mar 2007
Safety Issue?	Yes

Analysis Population Description
Safety population

Reporting Groups

	Description
Cetuximab Plus Chemotherapy	Subjects in will receive initial dose of 400 mg/m^2 cetuximab (over 2 hours) followed by weekly doses of 250 mg/m^2 (over 1 hour). All doses will be given by intravenous (IV) infusion. Subjects will receive either Cisplatin (100 mg/m^2 on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks or Carboplatin (Area under the curve (AUC) 5 IV on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks.
Chemotherapy Alone	All doses will be given by IV infusion. Subjects will receive either Cisplatin (100 mg/m^2 on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks or Carboplatin (AUC 5 IV on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks.

Measured Values

	Cetuximab Plus Chemotherapy	Chemotherapy Alone
Number of Participants Analyzed	219	215
Safety - Number of Patients Experiencing Any Adverse Event [units: participants]	218	208

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 Chemotherapy	Subjects in will receive initial dose of 400 mg/m^2 cetuximab (over 2 hours) followed by weekly doses of 250 mg/m^2 (over 1 hour). All doses will be given by intravenous (IV) infusion. Subjects will receive either Cisplatin (100 mg/m^2 on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks or Carboplatin (Area under the curve (AUC) 5 IV on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks.
Chemotherapy Alone	All doses will be given by IV infusion. Subjects will receive either Cisplatin (100 mg/m^2 on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks or Carboplatin (AUC 5 IV on day 1) + 5-FU (1000 mg/m^2 continuous IV from day 1 to day 4) every 3 weeks.

Serious Adverse Events

	Cetuximab Plus Chemotherapy	Chemotherapy Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Total	110/219 (50.23%)	102/215 (47.44%)
Blood and lymphatic system disorders		
Anaemia [A] †	5/219 (2.28%)	10/215 (4.65%)
Coagulopathy [A] †	1/219 (0.46%)	0/215 (0%)

	Cetuximab Plus Chemotherapy	Chemotherapy Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Febrile bone marrow aplasia [A] †	1/219 (0.46%)	1/215 (0.47%)
Febrile neutropenia [A] †	8/219 (3.65%)	9/215 (4.19%)
Haemolysis [A] †	0/219 (0%)	1/215 (0.47%)
Leukocytosis [A] †	0/219 (0%)	1/215 (0.47%)
Leukopenia [A] †	1/219 (0.46%)	5/215 (2.33%)
Lymph node pain [A] †	1/219 (0.46%)	0/215 (0%)
Neutropenia [A] †	3/219 (1.37%)	10/215 (4.65%)
Pancytopenia [A] †	1/219 (0.46%)	0/215 (0%)
Thrombocytopenia [A] †	4/219 (1.83%)	6/215 (2.79%)
Cardiac disorders		
Acute coronary syndrome [A] †	1/219 (0.46%)	0/215 (0%)
Acute myocardial infarction [A] †	2/219 (0.91%)	0/215 (0%)
Angina pectoris [A] †	0/219 (0%)	1/215 (0.47%)
Angina unstable [A] †	1/219 (0.46%)	0/215 (0%)
Arrhythmia [A] †	1/219 (0.46%)	1/215 (0.47%)
Arrhythmia supraventricular [A] †	0/219 (0%)	1/215 (0.47%)
Atrial fibrillation [A] †	0/219 (0%)	1/215 (0.47%)
Cardiac arrest [A] †	0/219 (0%)	2/215 (0.93%)
Cardiac failure [A] †	2/219 (0.91%)	1/215 (0.47%)
Cardio-respiratory arrest [A] †	0/219 (0%)	1/215 (0.47%)
Cardiopulmonary failure [A] †	2/219 (0.91%)	0/215 (0%)
Coronary artery thrombosis [A] †	0/219 (0%)	1/215 (0.47%)

	Cetuximab Plus Chemotherapy	Chemotherapy Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Myocardial infarction [A] †	2/219 (0.91%)	0/215 (0%)
Congenital, familial and genetic disorders		
Tracheo-oesophageal fistula [A] †	0/219 (0%)	1/215 (0.47%)
Eye disorders		
Keratitis [A] †	1/219 (0.46%)	0/215 (0%)
Gastrointestinal disorders		
Abdominal pain [A] †	2/219 (0.91%)	2/215 (0.93%)
Abdominal pain upper [A] †	1/219 (0.46%)	2/215 (0.93%)
Aphagia [A] †	0/219 (0%)	1/215 (0.47%)
Colitis [A] †	1/219 (0.46%)	0/215 (0%)
Constipation [A] †	0/219 (0%)	1/215 (0.47%)
Diarrhoea [A] †	4/219 (1.83%)	2/215 (0.93%)
Duodenal ulcer perforation [A] †	0/219 (0%)	1/215 (0.47%)
Dysphagia [A] †	2/219 (0.91%)	2/215 (0.93%)
Gastrointestinal haemorrhage [A] †	0/219 (0%)	1/215 (0.47%)
Haematemesis [A] †	1/219 (0.46%)	1/215 (0.47%)
Ileus [A] †	0/219 (0%)	1/215 (0.47%)
Melaena [A] †	0/219 (0%)	1/215 (0.47%)
Nausea [A] †	0/219 (0%)	1/215 (0.47%)
Oral pain [A] †	1/219 (0.46%)	0/215 (0%)
Rectal haemorrhage [A] †	0/219 (0%)	1/215 (0.47%)
Stomatitis [A] †	2/219 (0.91%)	0/215 (0%)

	Cetuximab Plus Chemotherapy	Chemotherapy Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Stress ulcer [A] †	0/219 (0%)	1/215 (0.47%)
Subileus [A] †	0/219 (0%)	1/215 (0.47%)
Upper gastrointestinal haemorrhage [A] †	1/219 (0.46%)	1/215 (0.47%)
Vomiting [A] †	5/219 (2.28%)	4/215 (1.86%)
General disorders		
Asthenia [A] †	2/219 (0.91%)	1/215 (0.47%)
Chest pain [A] †	0/219 (0%)	1/215 (0.47%)
Chills [A] †	0/219 (0%)	1/215 (0.47%)
Death [A] †	1/219 (0.46%)	1/215 (0.47%)
Face oedema [A] †	0/219 (0%)	1/215 (0.47%)
Fatigue [A] †	4/219 (1.83%)	2/215 (0.93%)
General physical health deterioration [A] †	5/219 (2.28%)	2/215 (0.93%)
Hyperthermia [A] †	0/219 (0%)	1/215 (0.47%)
Mucosal inflammation [A] †	5/219 (2.28%)	6/215 (2.79%)
Multi-organ failure [A] †	1/219 (0.46%)	0/215 (0%)
Oedema [A] †	1/219 (0.46%)	0/215 (0%)
Oedema peripheral [A] †	1/219 (0.46%)	0/215 (0%)
Performance status decreased [A] †	2/219 (0.91%)	4/215 (1.86%)
Pyrexia [A] †	2/219 (0.91%)	7/215 (3.26%)
Sudden death [A] †	2/219 (0.91%)	0/215 (0%)
Hepatobiliary disorders		
Hepatomegaly [A] †	0/219 (0%)	1/215 (0.47%)

	Cetuximab Plus Chemotherapy	Chemotherapy Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Hyperbilirubinaemia [A] †	1/219 (0.46%)	0/215 (0%)
Immune system disorders		
Anaphylactic reaction [A] †	1/219 (0.46%)	0/215 (0%)
Hypersensitivity [A] †	4/219 (1.83%)	0/215 (0%)
Infections and infestations		
Abscess neck [A] †	1/219 (0.46%)	0/215 (0%)
Bronchopneumonia [A] †	1/219 (0.46%)	1/215 (0.47%)
Catheter related infection [A] †	2/219 (0.91%)	0/215 (0%)
Catheter sepsis [A] †	1/219 (0.46%)	0/215 (0%)
Central line infection [A] †	1/219 (0.46%)	0/215 (0%)
Erysipelas [A] †	1/219 (0.46%)	0/215 (0%)
Gastroenteritis [A] †	1/219 (0.46%)	0/215 (0%)
Infection [A] †	2/219 (0.91%)	2/215 (0.93%)
Lower respiratory tract infection [A] †	0/219 (0%)	1/215 (0.47%)
Lung infection [A] †	0/219 (0%)	1/215 (0.47%)
Lymph gland infection [A] †	1/219 (0.46%)	0/215 (0%)
Meningitis [A] †	1/219 (0.46%)	0/215 (0%)
Neutropenic sepsis [A] †	0/219 (0%)	1/215 (0.47%)
Pharyngitis [A] †	1/219 (0.46%)	0/215 (0%)
Pneumococcal sepsis [A] †	1/219 (0.46%)	0/215 (0%)
Pneumonia [A] †	10/219 (4.57%)	4/215 (1.86%)
Pneumonia staphylococcal [A] †	0/219 (0%)	1/215 (0.47%)

	Cetuximab Plus Chemotherapy	Chemotherapy Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Pulmonary tuberculosis [A] †	1/219 (0.46%)	0/215 (0%)
Pyothorax [A] †	1/219 (0.46%)	0/215 (0%)
Respiratory tract infection [A] †	0/219 (0%)	2/215 (0.93%)
Salmonella sepsis [A] †	1/219 (0.46%)	0/215 (0%)
Sepsis [A] †	6/219 (2.74%)	1/215 (0.47%)
Septic shock [A] †	3/219 (1.37%)	0/215 (0%)
Staphylococcal infection [A] †	1/219 (0.46%)	0/215 (0%)
Thrombophlebitis septic [A] †	0/219 (0%)	1/215 (0.47%)
Injury, poisoning and procedural complications		
Feeding tube complication [A] †	1/219 (0.46%)	0/215 (0%)
Gastrostomy failure [A] †	0/219 (0%)	1/215 (0.47%)
Hip fracture [A] †	0/219 (0%)	1/215 (0.47%)
Post procedural haemorrhage [A] †	2/219 (0.91%)	1/215 (0.47%)
Investigations		
Blood creatinine increased [A] †	1/219 (0.46%)	1/215 (0.47%)
Creatinine renal clearance decreased [A] †	1/219 (0.46%)	0/215 (0%)
Haemoglobin [A] †	0/219 (0%)	1/215 (0.47%)
Haemoglobin decreased [A] †	0/219 (0%)	4/215 (1.86%)
Neurological examination abnormal [A] †	0/219 (0%)	1/215 (0.47%)
Oxygen saturation decreased [A] †	0/219 (0%)	1/215 (0.47%)
Platelet count decreased [A] †	1/219 (0.46%)	0/215 (0%)
Transaminases increased [A] †	1/219 (0.46%)	0/215 (0%)

	Cetuximab Plus Chemotherapy	Chemotherapy Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Urine electrolytes decreased [A] †	1/219 (0.46%)	0/215 (0%)
Weight decreased [A] †	1/219 (0.46%)	3/215 (1.4%)
Metabolism and nutrition disorders		
Anorexia [A] †	3/219 (1.37%)	0/215 (0%)
Cachexia [A] †	0/219 (0%)	1/215 (0.47%)
Dehydration [A] †	9/219 (4.11%)	3/215 (1.4%)
Diabetes mellitus [A] †	1/219 (0.46%)	0/215 (0%)
Hypercalcaemia [A] †	2/219 (0.91%)	1/215 (0.47%)
Hyperglycaemia [A] †	1/219 (0.46%)	3/215 (1.4%)
Hypernatraemia [A] †	0/219 (0%)	1/215 (0.47%)
Hyperuricaemia [A] †	0/219 (0%)	1/215 (0.47%)
Hypoalbuminaemia [A] †	0/219 (0%)	1/215 (0.47%)
Hypocalcaemia [A] †	4/219 (1.83%)	0/215 (0%)
Hypokalaemia [A] †	1/219 (0.46%)	0/215 (0%)
Hypomagnesaemia [A] †	4/219 (1.83%)	0/215 (0%)
Hyponatraemia [A] †	2/219 (0.91%)	1/215 (0.47%)
Hypophosphataemia [A] †	1/219 (0.46%)	0/215 (0%)
Hypovolaemia [A] †	0/219 (0%)	1/215 (0.47%)
Malnutrition [A] †	0/219 (0%)	1/215 (0.47%)
Musculoskeletal and connective tissue disorders		
Bursitis [A] †	1/219 (0.46%)	0/215 (0%)
Fistula [A] †	0/219 (0%)	2/215 (0.93%)

	Cetuximab Plus Chemotherapy	Chemotherapy Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Bladder cancer [A] †	0/219 (0%)	1/215 (0.47%)
Infected neoplasm [A] †	1/219 (0.46%)	1/215 (0.47%)
Malignant neoplasm progression [A] †	0/219 (0%)	1/215 (0.47%)
Neoplasm progression [A] †	1/219 (0.46%)	0/215 (0%)
Tumour associated fever [A] †	0/219 (0%)	1/215 (0.47%)
Tumour haemorrhage [A] †	2/219 (0.91%)	7/215 (3.26%)
Tumour pain [A] †	1/219 (0.46%)	0/215 (0%)
Nervous system disorders		
Brain oedema [A] †	1/219 (0.46%)	0/215 (0%)
Cerebral infarction [A] †	1/219 (0.46%)	0/215 (0%)
Cerebral ischaemia [A] †	1/219 (0.46%)	1/215 (0.47%)
Coma [A] †	0/219 (0%)	1/215 (0.47%)
Convulsion [A] †	2/219 (0.91%)	3/215 (1.4%)
Dizziness [A] †	2/219 (0.91%)	0/215 (0%)
Headache [A] †	1/219 (0.46%)	0/215 (0%)
Intracranial hypotension [A] †	0/219 (0%)	1/215 (0.47%)
Ischaemic stroke [A] †	0/219 (0%)	1/215 (0.47%)
Syncope [A] †	2/219 (0.91%)	3/215 (1.4%)
Psychiatric disorders		
Confusional state [A] †	1/219 (0.46%)	3/215 (1.4%)
Suicide attempt [A] †	0/219 (0%)	1/215 (0.47%)
Renal and urinary disorders		

	Cetuximab Plus Chemotherapy	Chemotherapy Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Haematuria [A] †	0/219 (0%)	1/215 (0.47%)
Renal failure [A] †	2/219 (0.91%)	2/215 (0.93%)
Renal failure acute [A] †	3/219 (1.37%)	3/215 (1.4%)
Respiratory, thoracic and mediastinal disorders		
Acute respiratory distress syndrome [A] †	0/219 (0%)	1/215 (0.47%)
Bronchial obstruction [A] †	0/219 (0%)	1/215 (0.47%)
Dyspnoea [A] †	4/219 (1.83%)	11/215 (5.12%)
Dyspnoea at rest [A] †	1/219 (0.46%)	0/215 (0%)
Haemoptysis [A] †	3/219 (1.37%)	1/215 (0.47%)
Hydropneumothorax [A] †	1/219 (0.46%)	0/215 (0%)
Laryngeal oedema [A] †	0/219 (0%)	1/215 (0.47%)
Lung disorder [A] †	1/219 (0.46%)	0/215 (0%)
Pleural effusion [A] †	0/219 (0%)	1/215 (0.47%)
Pneumonia aspiration [A] †	1/219 (0.46%)	1/215 (0.47%)
Pneumonitis [A] †	1/219 (0.46%)	2/215 (0.93%)
Pneumothorax [A] †	0/219 (0%)	2/215 (0.93%)
Productive cough [A] †	0/219 (0%)	2/215 (0.93%)
Pulmonary embolism [A] †	1/219 (0.46%)	0/215 (0%)
Pulmonary thrombosis [A] †	1/219 (0.46%)	0/215 (0%)
Respiratory failure [A] †	1/219 (0.46%)	5/215 (2.33%)
Stridor [A] †	0/219 (0%)	1/215 (0.47%)
Skin and subcutaneous tissue disorders		

	Cetuximab Plus Chemotherapy	Chemotherapy Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Dermatitis acneiform [A] †	1/219 (0.46%)	0/215 (0%)
Skin toxicity [A] †	1/219 (0.46%)	0/215 (0%)
Surgical and medical procedures		
Gastrostomy tube insertion [A] †	1/219 (0.46%)	0/215 (0%)
Medical device removal [A] †	1/219 (0.46%)	0/215 (0%)
Vascular disorders		
Aortic aneurysm [A] †	1/219 (0.46%)	0/215 (0%)
Aortic aneurysm rupture [A] †	1/219 (0.46%)	0/215 (0%)
Deep vein thrombosis [A] †	1/219 (0.46%)	1/215 (0.47%)
Haemorrhage [A] †	2/219 (0.91%)	1/215 (0.47%)
Hypertension [A] †	1/219 (0.46%)	0/215 (0%)
Hypotension [A] †	2/219 (0.91%)	2/215 (0.93%)
Ischaemia [A] †	1/219 (0.46%)	0/215 (0%)
Jugular vein thrombosis [A] †	1/219 (0.46%)	0/215 (0%)
Peripheral ischaemia [A] †	1/219 (0.46%)	0/215 (0%)
Shock [A] †	1/219 (0.46%)	0/215 (0%)
Shock haemorrhagic [A] †	1/219 (0.46%)	1/215 (0.47%)
Thrombosis [A] †	2/219 (0.91%)	1/215 (0.47%)
Wound haemorrhage [A] †	1/219 (0.46%)	0/215 (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 Chemotherapy	Chemotherapy Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Total	214/219 (97.72%)	198/215 (92.09%)
Blood and lymphatic system disorders		
Anaemia [A] †	92/219 (42.01%)	111/215 (51.63%)
Leukopenia [A] †	41/219 (18.72%)	32/215 (14.88%)
Lymphopenia [A] †	16/219 (7.31%)	13/215 (6.05%)
Neutropenia [A] †	83/219 (37.9%)	77/215 (35.81%)
Thrombocytopenia [A] †	46/219 (21%)	48/215 (22.33%)
Eye disorders		
Conjunctivitis [A] †	21/219 (9.59%)	0/215 (0%)
Gastrointestinal disorders		
Abdominal pain upper [A] †	13/219 (5.94%)	7/215 (3.26%)
Constipation [A] †	48/219 (21.92%)	43/215 (20%)
Diarrhoea [A] †	56/219 (25.57%)	33/215 (15.35%)
Dyspepsia [A] †	15/219 (6.85%)	7/215 (3.26%)
Dysphagia [A] †	21/219 (9.59%)	19/215 (8.84%)
Nausea [A] †	119/219 (54.34%)	100/215 (46.51%)
Stomatitis [A] †	31/219 (14.16%)	28/215 (13.02%)
Vomiting [A] †	84/219 (38.36%)	79/215 (36.74%)
General disorders		
Asthenia [A] †	56/219 (25.57%)	47/215 (21.86%)
Fatigue [A] †	49/219 (22.37%)	44/215 (20.47%)
General physical health deterioration [A] †	11/219 (5.02%)	2/215 (0.93%)

	Cetuximab Plus Chemotherapy	Chemotherapy Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Mucosal inflammation [A] †	50/219 (22.83%)	38/215 (17.67%)
Pyrexia [A] †	48/219 (21.92%)	23/215 (10.7%)
Infections and infestations		
Paronychia [A] †	19/219 (8.68%)	0/215 (0%)
Investigations		
Blood creatinine increased [A] †	11/219 (5.02%)	13/215 (6.05%)
Haemoglobin decreased [A] †	9/219 (4.11%)	11/215 (5.12%)
Platelet count decreased [A] †	13/219 (5.94%)	7/215 (3.26%)
Weight decreased [A] †	41/219 (18.72%)	30/215 (13.95%)
Metabolism and nutrition disorders		
Anorexia [A] †	54/219 (24.66%)	31/215 (14.42%)
Hyperkalaemia [A] †	12/219 (5.48%)	11/215 (5.12%)
Hypocalcaemia [A] †	26/219 (11.87%)	10/215 (4.65%)
Hypokalaemia [A] †	25/219 (11.42%)	15/215 (6.98%)
Hypomagnesaemia [A] †	22/219 (10.05%)	11/215 (5.12%)
Hyponatraemia [A] †	12/219 (5.48%)	17/215 (7.91%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Tumour pain [A] †	19/219 (8.68%)	19/215 (8.84%)
Nervous system disorders		
Dizziness [A] †	10/219 (4.57%)	11/215 (5.12%)
Headache [A] †	20/219 (9.13%)	15/215 (6.98%)
Insomnia [A] †	20/219 (9.13%)	7/215 (3.26%)
Peripheral sensory neuropathy [A] †	14/219 (6.39%)	8/215 (3.72%)

	Cetuximab Plus Chemotherapy	Chemotherapy Alone
	Affected/At Risk (%)	Affected/At Risk (%)
Respiratory, thoracic and mediastinal disorders		
Cough [A] †	22/219 (10.05%)	19/215 (8.84%)
Dyspnoea [A] †	19/219 (8.68%)	19/215 (8.84%)
Productive cough [A] †	12/219 (5.48%)	12/215 (5.58%)
Skin and subcutaneous tissue disorders		
Acne [A] †	48/219 (21.92%)	0/215 (0%)
Alopecia [A] †	27/219 (12.33%)	15/215 (6.98%)
Dermatitis acneiform [A] †	32/219 (14.61%)	0/215 (0%)
Dry skin [A] †	30/219 (13.7%)	1/215 (0.47%)
Exfoliative rash [A] †	17/219 (7.76%)	0/215 (0%)
Pruritus [A] †	18/219 (8.22%)	0/215 (0%)
Rash [A] †	61/219 (27.85%)	4/215 (1.86%)
Skin toxicity [A] †	13/219 (5.94%)	0/215 (0%)
Vascular disorders		
Hypertension [A] †	15/219 (6.85%)	10/215 (4.65%)
Hypotension [A] †	14/219 (6.39%)	9/215 (4.19%)
Phlebitis [A] †	11/219 (5.02%)	5/215 (2.33%)

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

Limitations and Caveats

Non-specific outcome measures 'Safety' & 'QOL assessments' were deleted from this entry in error.Replacement outcomes have been created. The 'Safety' 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.

Results Point of Contact:

Name/Official Title: Inmaculada Ollero/Clinical Trial Manager
Organization: Merck Serono
Phone: +34935655433
Email: iollero@merck.es