ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: 04/04/2014

ClinicalTrials.gov ID: NCT00820755

Study Identification

Unique Protocol ID:	EMR 62240-506
Brief Title:	Trial With Cetuximab in Maintenance Therapy After Platinum Based Chemotherapy in First Line Treatment of Non-small Cell Lung Cancer (NSCLC) (NEXT)
Official Title:	Open, Randomized, Multinational Phase IIIb Trial Evaluating the Activity and Safety of Cetuximab as 250 mg/m^2 Weekly and 500 mg/m^2 Every Two Weeks Maintenance Therapy After Platinum-based Chemotherapy in Combination With Cetuximab as First-line Treatment for Subjects With Advanced Non-small Cell Lung Cancer (NSCLC)
Secondary IDs:	

Study Status

Record Verification:	April 2014
Overall Status:	Completed
Study Start:	January 2009
Primary Completion:	December 2011 [Actual]
Study Completion:	June 2013 [Actual]

Sponsor/Collaborators

Sponsor:	Merck KGaA
Responsible Party:	Sponsor
Collaborators:	

Oversight

FDA Regulated?:	Yes
Applicable Trial?:	Section 801 Clinical Trial? No Delayed Posting? No
IND/IDE Protocol?:	No
Review Board:	Approval Status: Approved Approval Number: 266/2008 Board Name: Ethics committee of the Workplace Hospital Ruzinov in Bratislav - Slovakia Board Affiliation: Independent Phone: +421 2 48234 111 Email: fnspba@fnspba.sk
Data Monitoring?:	
Plan to Share Data?:	
Oversight Authorities:	Argentina: Administracion Nacional de Medicamentos, Alimentos y Tecnologia Medica Argentina: Human Research Bioethics Committee Australia: Department of Health and Ageing Therapeutic Goods Administration Australia: Human Research Ethics Committee Australia: National Health and Medical Research Council Austria: Agency for Health and Food Safety Austria: Ethikkommission Austria: Federal Ministry for Health and Women Belgium: Federal Agency for Medicines and Health Products, FAMHP Belgium: Federal Agency for Medicinal Products and Health Products Belgium: Institutional Review Board Belgium: Ministry of Social Affairs, Public Health and the Environment Belgium: The Federal Public Service (FPS) Health, Food Chain Safety and Environment Brazil: National Committee of Ethics in Research Brazil: Ministry of Health Brazil: National Health Surveillance Agency Chile: Comisión Nacional de Investigación Científica y Tecnológica Chile: Instituto de Salud Pública de Chile China: Ethics Committee China: Ministry of Health China: Food and Drug Administration Colombia: INVIMA Instituto Nacional de Vigilancia de Medicamentos y Alimentos Colombia: Institutional Review Board Czech Republic: State Institute for Drug Control European Union: European Medicines Agency France: Afssaps - Agence française de sécurité sanitaire des produits de santé (Saint-Denis) France: French Data Protection Authority

France: Institutional Ethical Committee
France: Ministry of Health
France: National Consultative Ethics Committee for Health and Life Sciences
Germany: Ethics Commission
Germany: Paul-Ehrlich-Institut
Greece: Ministry of Health and Welfare
Greece: National Organization of Medicines
Hong Kong: Department of Health
Hong Kong: Ethics Committee
Hong Kong: Joint CUHK-NTEC Clinical Research Ethics Committee
Hungary: National Institute of Pharmacy
India: Indian Council of Medical Research
India: Institutional Review Board
India: Ministry of Health
India: Science and Engineering Research Council
Ireland: Irish Medicines Board
Ireland: Medical Ethics Research Committee
Ireland: Ministry of Health
Israel: The Israel National Institute for Health Policy Research and Health Services Research
Israel: Ethics Commission
Israel: Israeli Health Ministry Pharmaceutical Administration
Israel: Ministry of Health
Italy: Ethics Committee
Italy: Ministry of Health
Italy: National Bioethics Committee
Italy: National Institute of Health
Italy: National Monitoring Centre for Clinical Trials - Ministry of Health
Italy: The Italian Medicines Agency
Korea: Food and Drug Administration
Mexico: Ethics Committee
Mexico: Federal Commission for Protection Against Health Risks
Mexico: Federal Commission for Sanitary Risks Protection
Mexico: Ministry of Health
Mexico: National Council of Science and Technology
Mexico: National Institute of Public Health, Health Secretariat
Netherlands: Independent Ethics Committee
Netherlands: Dutch Health Care Inspectorate
Netherlands: Medical Ethics Review Committee (METC)
Netherlands: Medicines Evaluation Board (MEB)
Netherlands: The Central Committee on Research Involving Human Subjects (CCMO)
Poland: Ministry of Health
Poland: Ministry of Science and Higher Education
Poland: Office for Registration of Medicinal Products, Medical Devices and Biocidal Products
Portugal: National Pharmacy and Medicines Institute
Russia: Ethics Committee

Russia: Ministry of Health of the Russian Federation
Russia: Pharmacological Committee, Ministry of Health
Singapore: Clinical Trials & Epidemiology Research Unit (CTERU)
Singapore: Domain Specific Review Boards
Singapore: Health Sciences Authority
Slovakia: State Institute for Drug Control
South Africa: Department of Health
South Africa: Medicines Control Council
South Africa: National Health Research Ethics Council
South Korea: Institutional Review Board
South Korea: Korea Food and Drug Administration (KFDA)
Spain: Comité Ético de Investigación Clínica
Spain: Ministry of Health
Spain: Ministry of Health and Consumption
Spain: Spanish Agency of Medicines
Sweden: Medical Products Agency
Sweden: Regional Ethical Review Board
Sweden: Swedish National Council on Medical Ethics
Sweden: The National Board of Health and Welfare
Switzerland: Ethikkommission
Switzerland: Federal Office of Public Health
Switzerland: Laws and standards
Switzerland: Swissmedic
Taiwan: Department of Health
Taiwan: Institutional Review Board
Taiwan: National Bureau of Controlled Drugs
Turkey: Ethics Committee
Turkey: Ministry of Health
United Kingdom: Medicines and Healthcare Products Regulatory Agency
United Kingdom: National Health Service
United Kingdom: Research Ethics Committee

Study Description

Brief Summary: This open-label, randomized, multinational, non-comparative, phase IIIb trial with 2 parallel groups will screen about 1400 subjects with stage IIIB non-small cell lung cancer (NSCLC) with pleural effusion or stage IV NSCLC. It is expected that of approximately 1200 (85 percent) subjects who will be included, about 1000 will be Caucasian; about 120 Asian, and the remainder (about 80) will be of other ethnic origin (that is neither Caucasian nor Asian). Approximately 480 (40 percent) subjects are expected to be free of progression at the end of combination treatment with cetuximab and platinum-based chemotherapy. These subjects will be eligible for randomization to intravenous cetuximab maintenance therapy with either 500 milligram per square meter (mg/m^2) every 2 weeks or 250 mg/m^2 weekly (q1w); about 240 subjects are expected per group.

The trial will be performed in a community practice setting, with approximately 230 centers participating in the trial worldwide (planned countries are Argentina, Australia, Austria, Belgium, Brazil, Chile, China, Colombia, Czech Republic, France, Germany,

Greece, Hong Kong, Hungary, India, Ireland, Israel, Italy, Mexico, Netherlands, Poland, Portugal, Russia, Singapore, Slovakia, South Africa, South Korea, Spain, Switzerland, Taiwan, Turkey, United Kingdom and Venezuela). With noncompetitive enrollment, approximately 4 to 8 subjects are expected to be enrolled at each center. Enrollment in the individual centers is generally limited to a maximum of 8 subjects. If any of these subjects does not receive trial treatment for any reason or discontinue all trial treatment at the first visit, additional subjects may be enrolled until 8 subjects were treated. The primary endpoint of the trial will be overall survival time from inclusion into the trial to death. Additional secondary efficacy endpoints will be time to treatment failure, tumor response, and disease control rate. Other endpoints will include safety and toxicity, compliance with maintenance therapy, subject satisfaction and translational research (TR) (for subjects with tumor samples available).

Detailed Description:

Conditions

Conditions: Non-Small Cell Lung Cancer (NSCLC)

Keywords:

Study Design

Study Type: Interventional

Primary Purpose: Treatment

Study Phase: Phase 3

Intervention Model: Parallel Assignment

Number of Arms: 3

Masking: Open Label

Allocation: Randomized

Endpoint Classification: Safety/Efficacy Study

Enrollment: 583 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Active Comparator: Cetuximab 250 mg/m^2 q1w + Platinum-based Doublet Chemotherapy	Drug: Cetuximab plus Platinum-based Doublet Chemotherapy Single first dose of cetuximab 400 mg/m^2 infusion will be administered intravenously over 120 minutes (min) followed by cetuximab 250 mg/m^2 intravenous infusion over 60 min q1w with background platinum-based doublet chemotherapy up to maximum of 6 cycles, until progressive disease, unacceptable toxicity, or withdrawal of consent. Platinum based

Arms	Assigned Interventions
	doublet chemotherapy will be administered as intravenous infusion as per study center included: vinorelbine 25 mg/m^2 on Day 1 (D1) and Day 8 (D8)+cisplatin 80 mg/m^2 on D1; or gemcitabine 1250 mg/m^2 on D1 and D8+cisplatin 75 mg/m^2 on D1; or gemcitabine 1000 mg/m^2 on D1 and D8+carboplatin at dose to reach area under curve (AUC)5 milligram*hour/milliliter (mg*hr/mL) on D1; or Docetaxel 75 mg/m^2 on D1+cisplatin 75 mg/m^2 on D1; or paclitaxel 175 mg/m^2 on D1+cisplatin 80 mg/m^2 on D1; or paclitaxel 200 mg/m^2 on D1+carboplatin at dose to reach AUC6 mg*hr/mL on D1, of each 3-week treatment cycle for a maximum of 6 cycles.
Active Comparator: Cetuximab 500 mg/m^2 every 2 weeks	Drug: Cetuximab 500 mg/m^2 Subjects who will be free of disease progression at the end of combination therapy, will enter in the maintenance therapy period. In the maintenance period, subjects will be receive cetuximab 500 mg/m^2 as intravenous infusion every 2 weeks, until progressive disease (PD), unacceptable toxicity, or withdrawal of consent. Other Names: • Erbitux
Active Comparator: Cetuximab 250 mg/m^2 weekly	Drug: Cetuximab 250 mg/m^2 Subjects who will free of disease progression at the end of combination therapy, will enter in the maintenance therapy period. In the maintenance period, subjects will be receive cetuximab 250 mg/m^2 as intravenous infusion weekly, until PD, unacceptable toxicity, or withdrawal of consent. Other Names: • Erbitux

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age:

Gender: Both

Accepts Healthy Volunteers?: No

Criteria: Inclusion Criteria:

- Subject has given written informed consent before any trial-related activities are carried out

- Male or female, greater than or equal to (>=)18 years of age at the time of informed consent, inpatient or outpatient
- Diagnosis of histologically or cytologically confirmed NSCLC, stage IIIB NSCLC with pleural effusion or stage IV
- Presence of at least 1 uni-dimensionally measurable index lesion, whereby index lesions must not lie in a previously irradiated area
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 at inclusion in the trial
- White blood count>= 3 * 10^9 per liter (/L) with neutrophils >= 1.5 * 10^9 /L , platelet count >=100 * 10^9 /L , and hemoglobin >= 5.6 millimole per liter (mmol/L) (9 gram per deciliter [g/dL])
- Total bilirubin less than or equal to (=<)1.5 * upper limit of normal (ULN) range
- Aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT) =< 5 * ULN
- Glomerular filtration rate (GFR) >=60 milliliter per minute (mL/min). The creatinine clearance (CrCl) estimated based on the Cockroft-Gault formula is used as a surrogate for the GFR
- Effective contraception that is, barrier method (condoms, diaphragm), oral, injectable or implant birth control, for both male and female subjects during the whole trial period and for at least 6 months after the end of trial treatment, if the risk of conception exists
- Recovered from relevant toxicities prior to inclusion in the trial

Exclusion Criteria:

- Previous exposure to Epidermal Growth Factor Receptor (EGFR)-targeting therapy
- Previous chemotherapy for NSCLC; neo-adjuvant or adjuvant (radio-)chemotherapy is allowed if it was finished 6 months prior to start of trial treatment
- Major surgery within 30 days prior to inclusion in the trial
- Prior chest irradiation within 90 days prior to inclusion in the trial (palliative radiation of bone lesions is allowed)
- Participation in another clinical trial or treatment with any investigational agent(s) within 30 days prior to inclusion in the trial
- Concurrent chronic systemic immune therapy, chemotherapy for disease other than cancer, or hormone therapy for the treatment of cancer not indicated in the trial protocol
- Documented or symptomatic brain metastasis
- Pre-existing ascites Grade >= 2 and/or pericardial effusion Grade >= 2
- Superior vena cava syndrome contra-indicating hydration
- Previous malignancy in the last 5 years except basal cell carcinoma of the skin or pre-invasive carcinoma of the cervix
- Active infection (infection requiring intravenous antibiotics), including active tuberculosis, known and declared human immunodeficiency virus (HIV)
- Myocardial infarction within 6 months prior to inclusion into the trial, uncontrolled congestive heart failure; or any current Grade 3 or 4 cardio-vascular disorder despite treatment
- Known hypersensitivity reaction to any of the components of trial treatments
- Symptomatic peripheral neuropathy National Cancer Institute-Common Toxicity Criteria (NCI-CTC) Grade >= 2 and/or ototoxicity Grade >= 2, except if due to trauma or mechanical impairment due to tumor mass
- History of significant neurologic or psychiatric disorders including dementia, seizures, bipolar disorder
- Medical or psychological condition that would not permit the subject to complete the trial or sign informed consent
- Legal incapacity or limited legal capacity
- Known drug abuse
- Pregnancy (absence to be confirmed by serum beta-human chorionic gonadotropin [beta-HCG test]) or lactation period

Contacts/Locations

Study Officials: Steffen Heeger, MD MSc
Study Director
Merck KGaA

Locations: Germany
Central Contact
Darmstadt, Germany

References

Citations:

Links:

Study Data/Documents:

Study Results

Participant Flow

Recruitment Details	First/last participants (informed consent): January 2009/17 March 2010. Clinical data cut-off: 17 December 2011
Pre-Assignment Details	Enrolled: 673 screened for eligibility; 90 excluded (mainly non-fulfillment of inclusion or exclusion criteria). 583 participants started.

Reporting Groups

	Description
Cetuximab 250 mg/m^2 q1w + Platinum-based Doublet Chemotherapy	Combination Phase: Single first dose of cetuximab 400 milligram per square meter (mg/m^2) infusion administered intravenously over 120 minutes (min) followed by cetuximab 250 mg/m^2 intravenous infusion over 60 min weekly (q1w) with background platinum-based doublet chemotherapy up to maximum of 6 cycles, until progressive disease, unacceptable toxicity, or withdrawal of consent. Platinum based doublet chemotherapy infusion intravenously as per study center included: vinorelbine 25 mg/m^2 on Day 1 (D1) and Day 8 (D8)+cisplatin 80 mg/m^2 on D1; or gemcitabine 1250 mg/m^2 on D1 and D8+cisplatin 75 mg/m^2 on D1; or gemcitabine 1000 mg/m^2 on D1 and D8+carboplatin at dose to reach area under curve (AUC)5 mg*hour/milliliter (mg*h/mL) on D1; or Docetaxel 75 mg/m^2 on D1+cisplatin 75 mg/m^2 on D1; or paclitaxel 175 mg/m^2 on D1+cisplatin 80 mg/m^2 on D1; or paclitaxel 200 mg/m^2 on D1+carboplatin at dose to reach AUC6 mg*h/mL on D1, of each 3-week treatment cycle for a maximum of 6 cycles.
Cetuximab 500 mg/m^2 Every 2 Weeks	Participants who were free of disease progression at the end of combination therapy, entered in the maintenance therapy period. In the maintenance period, participants received cetuximab 500 mg/m^2 as intravenous infusion every 2 weeks, until progressive disease (PD), unacceptable toxicity, or withdrawal of consent.
Cetuximab 250 mg/m^2 Weekly	Participants who were free of disease progression at the end of combination therapy, entered in the maintenance therapy period. In the maintenance period, participants received cetuximab 250 mg/m^2 as intravenous infusion weekly, until PD, unacceptable toxicity, or withdrawal of consent.

Period 1: Combination Therapy Phase

	Cetuximab 250 mg/m^2 q1w + Platinum-based Doublet Chemotherapy	Cetuximab 500 mg/ m^2 Every 2 Weeks	Cetuximab 250 mg/m^2 Weekly
Started	583	0	0
Completed	313 [1]	0	0
Not Completed	270	0	0
Adverse Event	77	0	0
Death	28	0	0
Protocol Violation	4	0	0
Lost to Follow-up	1	0	0
Withdrawal by Subject	21	0	0
Progressive disease	114	0	0
Sympt. deterioration w/o PD by imaging	14	0	0
Unspecified	11	0	0

[1] 2 of 313 participants excluded from maintenance phase analysis (reason: not eligible)

Period 2: Maintenance Therapy Phase

	Cetuximab 250 mg/m^2 q1w + Platinum-based Doublet Chemotherapy	Cetuximab 500 mg/ m^2 Every 2 Weeks	Cetuximab 250 mg/m^2 Weekly
Started	0	157	154
Completed	0	112	109
Not Completed	0	45	45
Investigational study phase ongoing	0	45	45

Baseline Characteristics

Reporting Groups

	Description
Cetuximab 250 mg/m^2 q1w + Platinum-based Doublet Chemotherapy	Combination Phase: Single first dose of cetuximab 400 milligram per square meter (mg/m^2) infusion administered intravenously over 120 minutes (min) followed by cetuximab 250 mg/m^2 intravenous infusion over 60 min weekly (q1w) with background platinum-based doublet chemotherapy up to maximum of 6 cycles, until progressive disease, unacceptable toxicity, or withdrawal of consent. Platinum based doublet chemotherapy infusion intravenously as per study center included: vinorelbine 25 mg/m^2 on Day 1 (D1) and Day 8 (D8)+cisplatin 80 mg/m^2 on D1; or gemcitabine 1250 mg/m^2 on D1 and D8+cisplatin 75 mg/m^2 on D1; or gemcitabine 1000 mg/m^2 on D1 and D8+carboplatin at dose to reach area under curve (AUC)5 mg*hour/milliliter (mg*h/mL) on D1; or Docetaxel 75 mg/m^2 on D1+cisplatin 75 mg/m^2 on D1; or paclitaxel 175 mg/m^2 on D1+cisplatin 80 mg/m^2 on D1; or paclitaxel 200 mg/m^2 on D1+carboplatin at dose to reach AUC6 mg*h/mL on D1, of each 3-week treatment cycle for a maximum of 6 cycles.

Baseline Measures

	Cetuximab 250 mg/m^2 q1w + Platinum-based Doublet Chemotherapy
Number of Participants	583
Age, Continuous [units: years] Mean (Standard Deviation)	60.4 (9.28)
Gender, Male/Female [units: participants]	
Female	147
Male	436

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Overall Survival (OS) Time
Measure Description	The OS time is defined as the time from trial inclusion to death. Participants without event are censored at the last date known to be alive or at the clinical cut-off date, whichever is earlier.
Time Frame	Time from trial inclusion to death or last day known to be alive, reported between day of first participant included, that is, Jan 2009 until cut-off date (17 Dec 2011)
Safety Issue?	No

Analysis Population Description

Intention-to-treat (ITT) maintenance analysis set included all participants who were included in ITT (all the participants enrolled in this study) analysis set, judged to be progression-free (based on computer tomography [CT] or magnetic resonance imaging [MRI] scan) by the Investigator and randomized to maintenance therapy.

Reporting Groups

	Description
Cetuximab 500 mg/m^2 Every 2 Weeks	Participants who were free of disease progression at the end of combination therapy, entered in the maintenance therapy period. In the maintenance period, participants received cetuximab 500 mg/m^2 as intravenous infusion every 2 weeks, until progressive disease (PD), unacceptable toxicity, or withdrawal of consent.
Cetuximab 250 mg/m^2 Weekly	Participants who were free of disease progression at the end of combination therapy, entered in the maintenance therapy period. In the maintenance period, participants received cetuximab 250 mg/m^2 as intravenous infusion weekly, until PD, unacceptable toxicity, or withdrawal of consent.

Measured Values

	Cetuximab 500 mg/m^2 Every 2 Weeks	Cetuximab 250 mg/m^2 Weekly
Number of Participants Analyzed	157	154
Overall Survival (OS) Time [units: months] Median (95% Confidence Interval)	16.1 (13.6 to 18.2)	15.5 (13.2 to 19.7)

2. Primary Outcome Measure:

Measure Title	Percentage of Participants With 1-year Overall Survival

Measure Description	The OS time is defined as the time from trial inclusion to death. Participants without event are censored at the last date known to be alive or at the clinical cut-off date, whichever is earlier. Percentage of participants who were still alive until one year after the last participant was included (March 2010).
Time Frame	Time from trial inclusion to death or last day known to be alive, reported between day of first participant included, that is, Jan 2009 until one year after the last participant was included (March 2010)
Safety Issue?	No

Analysis Population Description

ITT maintenance analysis set included all participants who were included in ITT (all the participants enrolled in this study) analysis set, judged to be progression-free (based on CT or MRI scan) by the Investigator and randomized to maintenance therapy.

Reporting Groups

	Description
Cetuximab 500 mg/m^2 Every 2 Weeks	Participants who were free of disease progression at the end of combination therapy, entered in the maintenance therapy period. In the maintenance period, participants received cetuximab 500 mg/m^2 as intravenous infusion every 2 weeks, until progressive disease (PD), unacceptable toxicity, or withdrawal of consent.
Cetuximab 250 mg/m^2 Weekly	Participants who were free of disease progression at the end of combination therapy, entered in the maintenance therapy period. In the maintenance period, participants received cetuximab 250 mg/m^2 as intravenous infusion weekly, until PD, unacceptable toxicity, or withdrawal of consent.

Measured Values

	Cetuximab 500 mg/m^2 Every 2 Weeks	Cetuximab 250 mg/m^2 Weekly
Number of Participants Analyzed	157	154
Percentage of Participants With 1-year Overall Survival [units: percentage of participants] Number (95% Confidence Interval)	62.8 (54.7 to 70.0)	64.4 (56.2 to 71.4)

3. Secondary Outcome Measure:

Measure Title	Overall Survival (OS) Time (From Randomization to Cetuximab Maintenance Regimen Until Death)
Measure Description	The OS time is defined as the time from randomization in cetuximab maintenance regimen to death. Participants without event are censored at the last date known to be alive or at the clinical cut-off date, whichever is earlier.
Time Frame	Time from randomization in cetuximab maintenance regimen to death or last day known to be alive, reported between day of first participant randomized, that is, May 2009 until cut-off date (17 Dec 2011)

Safety Issue?	No

Analysis Population Description

ITT maintenance analysis set included all participants who were included in ITT (all the participants enrolled in this study) analysis set, judged to be progression-free (based on CT or MRI scan) by the Investigator and randomized to maintenance therapy.

Reporting Groups

	Description
Cetuximab 500 mg/m^2 Every 2 Weeks	Participants who were free of disease progression at the end of combination therapy, entered in the maintenance therapy period. In the maintenance period, participants received cetuximab 500 mg/m^2 as intravenous infusion every 2 weeks, until progressive disease (PD), unacceptable toxicity, or withdrawal of consent.
Cetuximab 250 mg/m^2 Weekly	Participants who were free of disease progression at the end of combination therapy, entered in the maintenance therapy period. In the maintenance period, participants received cetuximab 250 mg/m^2 as intravenous infusion weekly, until PD, unacceptable toxicity, or withdrawal of consent.

Measured Values

	Cetuximab 500 mg/m^2 Every 2 Weeks	Cetuximab 250 mg/m^2 Weekly
Number of Participants Analyzed	157	154
Overall Survival (OS) Time (From Randomization to Cetuximab Maintenance Regimen Until Death) [units: months] Median (95% Confidence Interval)	12.6 (10.1 to 14.8)	12.6 (9.3 to 16.0)

Statistical Analysis 1 for Overall Survival (OS) Time (From Randomization to Cetuximab Maintenance Regimen Until Death)

Statistical Analysis Overview	Comparison Groups	Cetuximab 500 mg/m^2 Every 2 Weeks, Cetuximab 250 mg/m^2 Weekly
	Comments	Exploratory analysis to test the null hypothesis of no difference between maintenance therapy regimen. Model is adjusted by histology (interactive voice response system [IVRS]) and tumor response status at the end of combination therapy (‘complete response [CR] or partial response [PR]’ versus ‘other’).
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.1265
	Comments	[Not specified]

	Method	Log Rank
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio, log
	Estimated Value	0.959
	Confidence Interval	(2-Sided) 95% 0.736 to 1.250
	Estimation Comments	[Not specified]

4. Secondary Outcome Measure:

Measure Title	Time to Treatment Failure
Measure Description	Time to treatment failure is defined as the time from trial inclusion to date of either first occurrence of progression, discontinuation of treatment due to progression or adverse event, withdrawal of consent or lost to follow up, start of further anticancer therapy, or death, whichever is earlier. Participants without events are censored either at the time of their last drug intake, or on the day of inclusion (Day 1) if they received no study drug.
Time Frame	Time from trial inclusion to treatment failure or last drug intake, reported between day of first participant included, that is, Jan 2009 until cut-off date (17 Dec 2011)
Safety Issue?	No

Analysis Population Description

ITT maintenance analysis set included all participants who were included in ITT (all the participants enrolled in this study) analysis set, judged to be progression-free (based on CT or MRI scan) by the Investigator and randomized to maintenance therapy.

Reporting Groups

	Description
Cetuximab 500 mg/m^2 Every 2 Weeks	Participants who were free of disease progression at the end of combination therapy, entered in the maintenance therapy period. In the maintenance period, participants received cetuximab 500 mg/m^2 as intravenous infusion every 2 weeks, until progressive disease (PD), unacceptable toxicity, or withdrawal of consent.
Cetuximab 250 mg/m^2 Weekly	Participants who were free of disease progression at the end of combination therapy, entered in the maintenance therapy period. In the maintenance period, participants received cetuximab 250 mg/m^2 as intravenous infusion weekly, until PD, unacceptable toxicity, or withdrawal of consent.

Measured Values

	Cetuximab 500 mg/m^2 Every 2 Weeks	Cetuximab 250 mg/m^2 Weekly
Number of Participants Analyzed	157	154

	Cetuximab 500 mg/m^2 Every 2 Weeks	Cetuximab 250 mg/m^2 Weekly
Time to Treatment Failure [units: months] Median (95% Confidence Interval)	5.8 (5.6 to 6.6)	6.6 (6.1 to 6.9)

5. Secondary Outcome Measure:

Measure Title	Time to Treatment Failure (From Randomization to Cetuximab Maintenance Regimen Until Death)
Measure Description	Time from randomization in cetuximab maintenance regimen to date of either first occurrence of progression, discontinuation of treatment due to progression or adverse event, withdrawal of consent or lost to follow up, start of further anticancer therapy, or death, whichever is earlier. Participants without events are censored either at the time of their last drug intake, or on the day of randomization (Day 1 of maintenance therapy) if they received no study drug.
Time Frame	Time from randomization in cetuximab maintenance regimen to treatment failure or last drug intake, reported between day of first participant randomized, that is, May 2009 until cut-off date (17 Dec 2011)
Safety Issue?	No

Analysis Population Description

ITT maintenance analysis set included all participants who were included in ITT (all the participants enrolled in this study) analysis set, judged to be progression-free (based on CT or MRI scan) by the Investigator and randomized to maintenance therapy.

Reporting Groups

	Description
Cetuximab 500 mg/m^2 Every 2 Weeks	Participants who were free of disease progression at the end of combination therapy, entered in the maintenance therapy period. In the maintenance period, participants received cetuximab 500 mg/m^2 as intravenous infusion every 2 weeks, until progressive disease (PD), unacceptable toxicity, or withdrawal of consent.
Cetuximab 250 mg/m^2 Weekly	Participants who were free of disease progression at the end of combination therapy, entered in the maintenance therapy period. In the maintenance period, participants received cetuximab 250 mg/m^2 as intravenous infusion weekly, until PD, unacceptable toxicity, or withdrawal of consent.

Measured Values

	Cetuximab 500 mg/m^2 Every 2 Weeks	Cetuximab 250 mg/m^2 Weekly
Number of Participants Analyzed	157	154
Time to Treatment Failure (From Randomization to Cetuximab Maintenance Regimen Until Death) [units: months] Median (95% Confidence Interval)	2.6 (2.1 to 2.8)	2.8 (2.6 to 4.0)

Statistical Analysis 1 for Time to Treatment Failure (From Randomization to Cetuximab Maintenance Regimen Until Death)

Statistical Analysis Overview	Comparison Groups	Cetuximab 500 mg/m^2 Every 2 Weeks, Cetuximab 250 mg/m^2 Weekly
	Comments	Exploratory analysis to test the null hypothesis of no difference between maintenance therapy regimen. Model is adjusted by histology (IVRS) and tumor response status at the end of combination therapy ('CR or PR' versus 'other').
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0622
	Comments	[Not specified]
	Method	Log Rank
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	0.774
	Confidence Interval	(2-Sided) 95% 0.613 to 0.976
	Estimation Comments	[Not specified]

6. Secondary Outcome Measure:

Measure Title	Percentage of Participants With Best Unconfirmed Tumor Response in the Combination Therapy Phase
Measure Description	The response rate is defined as the percentage of participants having achieved complete response (CR) or partial response (PR) as the unconfirmed best overall response (BOR) according to centrally reviewed investigator assessments based on an independent review charter (IRC). As per Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.0) for target lesions and assessed by MRI: CR = Disappearance of all target lesions; PR = at least 30% decrease in the sum of the longest diameter of target lesions; Overall Response (OR) = CR + PR
Time Frame	Evaluations were performed every 2 cycles during combination therapy period until progression and at the end of combination therapy period, reported between day of first participant included, that is, Jan 2009, until cut-off date, (17 Dec 2011)
Safety Issue?	No

Analysis Population Description

ITT analysis set included all participants enrolled in this study.

Reporting Groups

	Description
Cetuximab 250 mg/m^2 q1w + Platinum-based Doublet Chemotherapy	Combination Phase: Single first dose of cetuximab 400 milligram per square meter (mg/m^2) infusion administered intravenously over 120 minutes (min) followed by cetuximab 250 mg/m^2 intravenous infusion over 60 min weekly (q1w) with background platinum-based doublet chemotherapy up to maximum of 6 cycles, until progressive disease, unacceptable toxicity, or withdrawal of consent. Platinum based doublet chemotherapy infusion intravenously as per study center included: vinorelbine 25 mg/m^2 on Day 1 (D1) and Day 8 (D8)+cisplatin 80 mg/m^2 on D1; or gemcitabine 1250 mg/m^2 on D1 and D8+cisplatin 75 mg/m^2 on D1; or gemcitabine 1000 mg/m^2 on D1 and D8+carboplatin at dose to reach area under curve (AUC)5 mg*hour/milliliter (mg*h/mL) on D1; or Docetaxel 75 mg/m^2 on D1+cisplatin 75 mg/m^2 on D1; or paclitaxel 175 mg/m^2 on D1+cisplatin 80 mg/m^2 on D1; or paclitaxel 200 mg/m^2 on D1+carboplatin at dose to reach AUC6 mg*h/mL on D1, of each 3-week treatment cycle for a maximum of 6 cycles.

Measured Values

	Cetuximab 250 mg/m^2 q1w + Platinum-based Doublet Chemotherapy
Number of Participants Analyzed	583
Percentage of Participants With Best Unconfirmed Tumor Response in the Combination Therapy Phase [units: percentage of participants] Number (95% Confidence Interval)	36.2 (32.3 to 40.2)

7. Secondary Outcome Measure:

Measure Title	Percentage of Participant With Best Unconfirmed Tumor Response for the Whole Study Period
Measure Description	The response rate is defined as the percentage of participants having achieved CR and PR as the BOR according to IRC assessment in combination therapy phase and radiological assessments (based on response evaluation criteria in solid tumors [RECIST] Version 1.0) in the maintenance therapy phase. As per RECIST v1.0 for target lesions and assessed by MRI: CR = Disappearance of all target lesions; PR = at least 30% decrease in the sum of the longest diameter of target lesions; Overall Response (OR) = CR + PR
Time Frame	Evaluations were performed every 2 cycles during combination therapy and 6-weekly during maintenance therapy period until progression and at end of both periods, reported between day of first participant included, Jan 2009 until cut-off date (17 Dec 2011)
Safety Issue?	No

Analysis Population Description

ITT maintenance analysis set included all participants who were included in ITT (all the participants enrolled in this study) analysis set, judged to be progression-free (based on CT or MRI scan) by the Investigator and randomized to maintenance therapy.

Reporting Groups

	Description
Cetuximab 500 mg/m^2 Every 2 Weeks	Participants who were free of disease progression at the end of combination therapy, entered in the maintenance therapy period. In the maintenance period, participants received cetuximab 500 mg/m^2 as intravenous infusion every 2 weeks, until progressive disease (PD), unacceptable toxicity, or withdrawal of consent.
Cetuximab 250 mg/m^2 Weekly	Participants who were free of disease progression at the end of combination therapy, entered in the maintenance therapy period. In the maintenance period, participants received cetuximab 250 mg/m^2 as intravenous infusion weekly, until PD, unacceptable toxicity, or withdrawal of consent.

Measured Values

	Cetuximab 500 mg/m^2 Every 2 Weeks	Cetuximab 250 mg/m^2 Weekly
Number of Participants Analyzed	157	154
Percentage of Participant With Best Unconfirmed Tumor Response for the Whole Study Period [units: percentage of participants] Number (95% Confidence Interval)	54.8 (46.6 to 62.7)	57.8 (49.6 to 65.7)

8. Secondary Outcome Measure:

Measure Title	Percentage of Participants With Disease Control in the Combination Therapy Phase
Measure Description	The disease control rate is defined as the percentage of participants having achieved complete response or partial response or stable disease as the unconfirmed BOR according to IRC assessment.
Time Frame	Evaluations were performed every 2 cycles during combination therapy period until progression and at the end of combination therapy period, reported between day of first participant included, that is, Jan 2009, until cut-off date, (17 Dec 2011)
Safety Issue?	No

Analysis Population Description

ITT analysis set included all participants enrolled in this study.

Reporting Groups

	Description
Cetuximab 250 mg/m^2 q1w + Platinum-based Doublet Chemotherapy	Combination Phase: Single first dose of cetuximab 400 milligram per square meter (mg/m^2) infusion administered intravenously over 120 minutes (min) followed by cetuximab 250 mg/m^2 intravenous infusion over 60 min weekly (q1w) with background platinum-based doublet chemotherapy up to maximum of 6 cycles, until progressive disease, unacceptable toxicity, or withdrawal of consent. Platinum based doublet chemotherapy infusion intravenously as per study center included: vinorelbine 25 mg/m^2 on Day 1 (D1) and Day 8 (D8)+cisplatin 80 mg/m^2 on D1; or gemcitabine 1250 mg/m^2 on D1 and D8+cisplatin 75 mg/m^2 on D1; or gemcitabine 1000 mg/m^2 on D1 and D8+carboplatin at dose to reach area under curve (AUC)5 mg*hour/milliliter (mg*h/mL) on D1; or Docetaxel 75 mg/m^2 on D1+cisplatin 75 mg/m^2 on D1; or paclitaxel 175 mg/m^2 on D1+cisplatin 80 mg/m^2 on D1; or paclitaxel 200 mg/m^2 on D1+carboplatin at dose to reach AUC6 mg*h/mL on D1, of each 3-week treatment cycle for a maximum of 6 cycles.

Measured Values

	Cetuximab 250 mg/m^2 q1w + Platinum-based Doublet Chemotherapy
Number of Participants Analyzed	583
Percentage of Participants With Disease Control in the Combination Therapy Phase [units: percentage of participants] Number (95% Confidence Interval)	65.7 (61.7 to 69.5)

9. Secondary Outcome Measure:

Measure Title	Percentage of Participants With Disease Control for the Whole Study Period
Measure Description	The disease control rate is defined as the percentage of participants having achieved complete response or partial response or stable disease as the unconfirmed best overall response according to IRC assessment in combination therapy phase and radiological assessments (based on RECIST Version 1.0 criteria) in the maintenance therapy phase.
Time Frame	Evaluations were performed every 2 cycles during combination therapy and 6-weekly during maintenance therapy period until progression and at end of both periods, reported between day of first participant included, Jan 2009 until cut-off date (17 Dec 2011)
Safety Issue?	No

Analysis Population Description

ITT maintenance analysis set included all participants who were included in ITT (all the participants enrolled in this study) analysis set, judged to be progression-free (based on CT or MRI scan) by the Investigator and randomized to maintenance therapy.

Reporting Groups

	Description
Cetuximab 500 mg/m^2 Every 2 Weeks	Participants who were free of disease progression at the end of combination therapy, entered in the maintenance therapy period. In the maintenance period, participants received cetuximab 500 mg/m^2 as intravenous infusion every 2 weeks, until progressive disease (PD), unacceptable toxicity, or withdrawal of consent.
Cetuximab 250 mg/m^2 Weekly	Participants who were free of disease progression at the end of combination therapy, entered in the maintenance therapy period. In the maintenance period, participants received cetuximab 250 mg/m^2 as intravenous infusion weekly, until PD, unacceptable toxicity, or withdrawal of consent.

Measured Values

	Cetuximab 500 mg/m^2 Every 2 Weeks	Cetuximab 250 mg/m^2 Weekly
Number of Participants Analyzed	157	154
Percentage of Participants With Disease Control for the Whole Study Period [units: percentage of participants] Number (95% Confidence Interval)	98.7 (95.5 to 99.8)	99.4 (96.4 to 100)

Reported Adverse Events

Time Frame	Time from Baseline up to 30 days after the last dose of study treatment.
Additional Description	One participant who was randomized to ‘Cetuximab 500 mg/m^2 Every 2 Weeks’ arm actually received ‘Cetuximab 250 mg/m^2 Weekly’ treatment and was counted in this group for safety analysis

Reporting Groups

	Description
Cetuximab 250 mg/m^2 q1w + Platinum-based Doublet Chemotherapy	Combination Phase: Single first dose of cetuximab 400 milligram per square meter (mg/m^2) infusion administered intravenously over 120 minutes (min) followed by cetuximab 250 mg/m^2 intravenous infusion over 60 min weekly (q1w) with background platinum-based doublet chemotherapy up to maximum of 6 cycles, until progressive disease, unacceptable toxicity, or withdrawal of consent. Platinum based doublet chemotherapy infusion intravenously as per study center included: vinorelbine 25 mg/m^2 on Day 1 (D1) and Day 8 (D8)+cisplatin 80 mg/m^2 on D1; or gemcitabine 1250 mg/m^2 on D1 and D8+cisplatin 75 mg/m^2 on D1; or gemcitabine 1000 mg/m^2 on D1 and D8+carboplatin at dose to reach area under curve (AUC)5 mg*hour/milliliter (mg*h/mL) on D1; or Docetaxel 75 mg/m^2 on D1+cisplatin 75 mg/m^2 on D1; or paclitaxel 175 mg/m^2 on D1+cisplatin 80 mg/m^2 on D1; or paclitaxel 200 mg/m^2 on D1+carboplatin at dose to reach AUC6 mg*h/mL on D1, of each 3-week treatment cycle for a maximum of 6 cycles.
Cetuximab 500 mg/m^2 Every 2 Weeks	Participants who were free of disease progression after combination therapy, they administered with cetuximab 500 mg/m^2 intravenously for 2 weeks, for up to PD, development of unacceptable toxicities, or withdrawal of consent after the end of combination therapy.
Cetuximab 250 mg/m^2 Weekly	Participants who were free of disease progression at the end of combination therapy, entered in the maintenance therapy period. In the maintenance period, participants received cetuximab 250 mg/m^2 as intravenous infusion weekly, until PD, unacceptable toxicity, or withdrawal of consent.

Serious Adverse Events

	Cetuximab 250 mg/m^2 q1w + Platinum-based Doublet Chemotherapy	Cetuximab 500 mg/ m^2 Every 2 Weeks	Cetuximab 250 mg/m^2 Weekly
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	243/583 (41.68%)	30/156 (19.23%)	33/155 (21.29%)
Blood and lymphatic system disorders			
Anaemia [A] *	6/583 (1.03%)	1/156 (0.64%)	1/155 (0.65%)
Bone marrow failure [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Febdrile bone marrow aplasia [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Febrile Neutropenia [A] *	20/583 (3.43%)	0/156 (0%)	0/155 (0%)
Granulocytopenia [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Leukocytosis [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Leukopenia [A] *	8/583 (1.37%)	0/156 (0%)	0/155 (0%)

	Cetuximab 250 mg/m^2 q1w + Platinum-based Doublet Chemotherapy	Cetuximab 500 mg/ m^2 Every 2 Weeks	Cetuximab 250 mg/m^2 Weekly
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Neutropenia [A] *	32/583 (5.49%)	1/156 (0.64%)	0/155 (0%)
Pancytopenia [A] *	4/583 (0.69%)	0/156 (0%)	1/155 (0.65%)
Thrombocytopenia [A] *	13/583 (2.23%)	0/156 (0%)	0/155 (0%)
Cardiac disorders			
Acute myocardial infarction [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Angina unstable [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Arrhythmia superaventricular [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Atrial fibrillation [A] *	3/583 (0.51%)	0/156 (0%)	0/155 (0%)
Cardiac arrest [A] *	1/583 (0.17%)	0/156 (0%)	1/155 (0.65%)
Cardiac failure [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Cardiac failure congestive [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Cardiovascular insufficiency [A] *	1/583 (0.17%)	0/156 (0%)	1/155 (0.65%)
Electromechanical dissociation [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Myocardial infarction [A] *	2/583 (0.34%)	1/156 (0.64%)	0/155 (0%)
Pericardial effusion [A] *	1/583 (0.17%)	1/156 (0.64%)	1/155 (0.65%)
Pericarditis [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Right ventricular dysfunction [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Sinus tachycardia [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Supraventricular tachycardia [A] *	1/583 (0.17%)	1/156 (0.64%)	0/155 (0%)
Tachycardia [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Congenital, familial and genetic disorders			

	Cetuximab 250 mg/m^2 q1w + Platinum-based Doublet Chemotherapy	Cetuximab 500 mg/ m^2 Every 2 Weeks	Cetuximab 250 mg/m^2 Weekly
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Aplasia [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Endocrine disorders			
Adrenal insufficiency [A] *	0/583 (0%)	0/156 (0%)	1/155 (0.65%)
Eye disorders			
Diplopia [A] *	0/583 (0%)	0/156 (0%)	1/155 (0.65%)
Gastrointestinal disorders			
Abdominal distension [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Abdominal pain [A] *	2/583 (0.34%)	0/156 (0%)	0/155 (0%)
Constipation [A] *	1/583 (0.17%)	0/156 (0%)	2/155 (1.29%)
Diarrhoea [A] *	9/583 (1.54%)	0/156 (0%)	0/155 (0%)
Duodenal ulcer [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Dyspepsia [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Dysphagia [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Gastrointestinal haemorrhage [A] *	2/583 (0.34%)	0/156 (0%)	0/155 (0%)
Haematemesis [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Haemorrhoids [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Large intestine perforation [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Melaena [A] *	0/583 (0%)	0/156 (0%)	1/155 (0.65%)
Mesenteric artery thrombosis [A] *	0/583 (0%)	1/156 (0.64%)	0/155 (0%)
Nausea [A] *	2/583 (0.34%)	0/156 (0%)	0/155 (0%)
Pancreatitis [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)

	Cetuximab 250 mg/m^2 q1w + Platinum-based Doublet Chemotherapy	Cetuximab 500 mg/ m^2 Every 2 Weeks	Cetuximab 250 mg/m^2 Weekly
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Rectal haemorrhage [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Reflux oesophagitis [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Small intestinal obstruction [A] *	0/583 (0%)	0/156 (0%)	1/155 (0.65%)
Stomatitis [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Vomiting [A] *	11/583 (1.89%)	0/156 (0%)	1/155 (0.65%)
General disorders			
Asthenia [A] *	8/583 (1.37%)	1/156 (0.64%)	0/155 (0%)
Death [A] *	3/583 (0.51%)	2/156 (1.28%)	0/155 (0%)
Device leakage [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Disease progression [A] *	2/583 (0.34%)	2/156 (1.28%)	1/155 (0.65%)
Fatigue [A] *	6/583 (1.03%)	0/156 (0%)	1/155 (0.65%)
General physical health deterioration [A] *	4/583 (0.69%)	1/156 (0.64%)	0/155 (0%)
Infusion related reaction [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Multi-organ failure [A] *	2/583 (0.34%)	0/156 (0%)	0/155 (0%)
Non-cardiac chest pain [A] *	0/583 (0%)	1/156 (0.64%)	0/155 (0%)
Oedema peripheral [A] *	0/583 (0%)	1/156 (0.64%)	0/155 (0%)
Organ failure [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Pain [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Pyrexia [A] *	9/583 (1.54%)	0/156 (0%)	1/155 (0.65%)
Hepatobiliary disorders			
Hepatic failure [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)

	Cetuximab 250 mg/m^2 q1w + Platinum-based Doublet Chemotherapy	Cetuximab 500 mg/ m^2 Every 2 Weeks	Cetuximab 250 mg/m^2 Weekly
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Immune system disorders			
Anaphylactic reaction [A] *	3/583 (0.51%)	0/156 (0%)	0/155 (0%)
Anaphylactic shock [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Drug hypersensitivity [A] *	8/583 (1.37%)	0/156 (0%)	0/155 (0%)
Hypersensitivity [A] *	2/583 (0.34%)	0/156 (0%)	0/155 (0%)
Infections and infestations			
Anorectal infection [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Bronchitis [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Bronchopneumonia [A] *	0/583 (0%)	1/156 (0.64%)	0/155 (0%)
Cellulitis [A] *	2/583 (0.34%)	0/156 (0%)	0/155 (0%)
Device related infection [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Empyema [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Endocarditis [A] *	0/583 (0%)	1/156 (0.64%)	0/155 (0%)
Febrile infection [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Herpes zoster [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Kidney infection [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Lower respiratory tract infection [A] *	5/583 (0.86%)	0/156 (0%)	0/155 (0%)
Lower respiratory tract infection bacterial [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Lung infection [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Neutropenic infection [A] *	0/583 (0%)	0/156 (0%)	1/155 (0.65%)
Neutropenic sepsis [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)

	Cetuximab 250 mg/m^2 q1w + Platinum-based Doublet Chemotherapy	Cetuximab 500 mg/ m^2 Every 2 Weeks	Cetuximab 250 mg/m^2 Weekly
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Pneumonia [A] *	17/583 (2.92%)	4/156 (2.56%)	4/155 (2.58%)
Pseudomembranous colitis [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Pulmonary tuberculosis [A] *	0/583 (0%)	0/156 (0%)	1/155 (0.65%)
Pyothorax [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Respiratory tract infection [A] *	2/583 (0.34%)	0/156 (0%)	0/155 (0%)
Sepsis [A] *	3/583 (0.51%)	1/156 (0.64%)	0/155 (0%)
Septic shock [A] *	2/583 (0.34%)	0/156 (0%)	0/155 (0%)
Skin infection [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Subcutaneous abscess [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Upper respiratory tract infection [A] *	0/583 (0%)	2/156 (1.28%)	1/155 (0.65%)
Urinary tract infection [A] *	2/583 (0.34%)	2/156 (1.28%)	0/155 (0%)
Injury, poisoning and procedural complications			
Anastomotic ulcer [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Femur fracture [A] *	0/583 (0%)	0/156 (0%)	1/155 (0.65%)
Operative haemorrhage [A] *	0/583 (0%)	0/156 (0%)	1/155 (0.65%)
Renal injury [A] *	0/583 (0%)	1/156 (0.64%)	0/155 (0%)
Investigations			
Alanine aminotransferase increased [A] *	1/583 (0.17%)	0/156 (0%)	1/155 (0.65%)
Blood creatinine increased [A] *	2/583 (0.34%)	1/156 (0.64%)	0/155 (0%)
C-Reactive protein increased [A] *	2/583 (0.34%)	0/156 (0%)	0/155 (0%)
Neutrophil count decreased [A] *	3/583 (0.51%)	0/156 (0%)	0/155 (0%)

	Cetuximab 250 mg/m^2 q1w + Platinum-based Doublet Chemotherapy	Cetuximab 500 mg/ m^2 Every 2 Weeks	Cetuximab 250 mg/m^2 Weekly
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Platelet count decreased [A] *	5/583 (0.86%)	0/156 (0%)	0/155 (0%)
White blood cell count decreased [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Metabolism and nutrition disorders			
Decreased appetite [A] *	4/583 (0.69%)	0/156 (0%)	0/155 (0%)
Dehydration [A] *	4/583 (0.69%)	0/156 (0%)	0/155 (0%)
Electrolyte imbalance [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Hypercalcaemia [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Hyperglycaemia [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Hyperkalaemia [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Hypocalcaemia [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Hypoglycaemia [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Hypokalaemia [A] *	2/583 (0.34%)	0/156 (0%)	0/155 (0%)
Hypomagnesaemia [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Hyponatraemia [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Musculoskeletal and connective tissue disorders			
Arthralgia [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Back pain [A] *	5/583 (0.86%)	0/156 (0%)	0/155 (0%)
Bone pain [A] *	4/583 (0.69%)	0/156 (0%)	0/155 (0%)
Fasciitis [A] *	0/583 (0%)	0/156 (0%)	1/155 (0.65%)
Neck pain [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Pain in extremity [A] *	0/583 (0%)	0/156 (0%)	1/155 (0.65%)

	Cetuximab 250 mg/m^2 q1w + Platinum-based Doublet Chemotherapy	Cetuximab 500 mg/ m^2 Every 2 Weeks	Cetuximab 250 mg/m^2 Weekly
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant pleural effusion [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Metastases to central nervous system [A] *	0/583 (0%)	0/156 (0%)	1/155 (0.65%)
Neoplasm progression [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Pericardial effusion malignant [A] *	1/583 (0.17%)	0/156 (0%)	1/155 (0.65%)
Tumour associated fever [A] *	0/583 (0%)	1/156 (0.64%)	0/155 (0%)
Nervous system disorders			
Altered state of consciousness [A] *	0/583 (0%)	1/156 (0.64%)	0/155 (0%)
Cerebral ischaemia [A] *	3/583 (0.51%)	1/156 (0.64%)	0/155 (0%)
Cerebrovascular accident [A] *	3/583 (0.51%)	0/156 (0%)	0/155 (0%)
Cognitive disorder [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Convulsion [A] *	1/583 (0.17%)	1/156 (0.64%)	1/155 (0.65%)
Dementia Alzheimer's type [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Depressed level of consciousness [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Dizziness [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Headache [A] *	0/583 (0%)	1/156 (0.64%)	0/155 (0%)
Ischaemic stroke [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Mental impairment [A] *	0/583 (0%)	1/156 (0.64%)	0/155 (0%)
Pyramidal tract syndrome [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Spinal cord compression [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Syncope [A] *	2/583 (0.34%)	0/156 (0%)	0/155 (0%)

	Cetuximab 250 mg/m^2 q1w + Platinum-based Doublet Chemotherapy	Cetuximab 500 mg/ m^2 Every 2 Weeks	Cetuximab 250 mg/m^2 Weekly
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Transient ischaemic attack [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Psychiatric disorders			
Disorientation [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Renal and urinary disorders			
Haematuria [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Renal failure [A] *	2/583 (0.34%)	0/156 (0%)	0/155 (0%)
Renal failure acute [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure [A] *	2/583 (0.34%)	0/156 (0%)	0/155 (0%)
Bronchostenosis [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Dyspnoea [A] *	10/583 (1.72%)	2/156 (1.28%)	2/155 (1.29%)
Epistaxis [A] *	3/583 (0.51%)	0/156 (0%)	1/155 (0.65%)
Haemoptysis [A] *	5/583 (0.86%)	0/156 (0%)	1/155 (0.65%)
Hydropneumothorax [A] *	0/583 (0%)	1/156 (0.64%)	0/155 (0%)
Interstitial lung disease [A] *	0/583 (0%)	1/156 (0.64%)	0/155 (0%)
Pleural effusion [A] *	6/583 (1.03%)	2/156 (1.28%)	2/155 (1.29%)
Pneumonitis [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Pneumothorax [A] *	5/583 (0.86%)	0/156 (0%)	0/155 (0%)
Pulmonary embolism [A] *	12/583 (2.06%)	0/156 (0%)	1/155 (0.65%)
Pulmonary haemorrhage [A] *	2/583 (0.34%)	0/156 (0%)	1/155 (0.65%)
Respiratory acidosis [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)

	Cetuximab 250 mg/m^2 q1w + Platinum-based Doublet Chemotherapy	Cetuximab 500 mg/ m^2 Every 2 Weeks	Cetuximab 250 mg/m^2 Weekly
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Respiratory distress [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Respiratory failure [A] *	2/583 (0.34%)	0/156 (0%)	0/155 (0%)
Skin and subcutaneous tissue disorders			
Dermatitis acneiform [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Pruritus generalised [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Rash [A] *	1/583 (0.17%)	0/156 (0%)	1/155 (0.65%)
Vascular disorders			
Aortic thrombosis [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Arterial thrombosis [A] *	0/583 (0%)	0/156 (0%)	1/155 (0.65%)
Circulatory collapse [A] *	0/583 (0%)	0/156 (0%)	1/155 (0.65%)
Deep vein thrombosis [A] *	3/583 (0.51%)	0/156 (0%)	1/155 (0.65%)
Femoral artery embolism [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)
Hypertension [A] *	2/583 (0.34%)	0/156 (0%)	0/155 (0%)
Hypotension [A] *	2/583 (0.34%)	0/156 (0%)	0/155 (0%)
Peripheral ischaemia [A] *	3/583 (0.51%)	1/156 (0.64%)	0/155 (0%)
Thrombophlebitis [A] *	1/583 (0.17%)	0/156 (0%)	0/155 (0%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA 14.0

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 0%

	Cetuximab 250 mg/m^2 q1w + Platinum-based Doublet Chemotherapy	Cetuximab 500 mg/ m^2 Every 2 Weeks	Cetuximab 250 mg/m^2 Weekly
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	564/583 (96.74%)	121/156 (77.56%)	136/155 (87.74%)
Blood and lymphatic system disorders			
Anaemia [A] *	134/583 (22.98%)	9/156 (5.77%)	15/155 (9.68%)
Leukopenia [A] *	72/583 (12.35%)	0/156 (0%)	0/155 (0%)
Neutropenia [A] *	208/583 (35.68%)	0/156 (0%)	0/155 (0%)
Thrombocytopenia [A] *	112/583 (19.21%)	0/156 (0%)	0/155 (0%)
Ear and labyrinth disorders			
Tinnitus [A] *	13/583 (2.23%)	0/156 (0%)	0/155 (0%)
Eye disorders			
Conjunctivitis [A] *	0/583 (0%)	7/156 (4.49%)	10/155 (6.45%)
Gastrointestinal disorders			
Abdominal pain [A] *	21/583 (3.6%)	0/156 (0%)	0/155 (0%)
Abdominal pain upper [A] *	31/583 (5.32%)	0/156 (0%)	0/155 (0%)
Constipation [A] *	109/583 (18.7%)	3/156 (1.92%)	12/155 (7.74%)
Diarrhoea [A] *	120/583 (20.58%)	6/156 (3.85%)	15/155 (9.68%)
Dyspepsia [A] *	36/583 (6.17%)	0/156 (0%)	0/155 (0%)
Nausea [A] *	212/583 (36.36%)	3/156 (1.92%)	9/155 (5.81%)
Odynophagia [A] *	5/583 (0.86%)	0/156 (0%)	0/155 (0%)
Stomatitis [A] *	47/583 (8.06%)	0/156 (0%)	0/155 (0%)
Vomiting [A] *	122/583 (20.93%)	2/156 (1.28%)	8/155 (5.16%)
General disorders			

	Cetuximab 250 mg/m^2 q1w + Platinum-based Doublet Chemotherapy	Cetuximab 500 mg/ m^2 Every 2 Weeks	Cetuximab 250 mg/m^2 Weekly
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Asthenia [A] *	124/583 (21.27%)	6/156 (3.85%)	16/155 (10.32%)
Chills [A] *	16/583 (2.74%)	0/156 (0%)	0/155 (0%)
Fatigue [A] *	114/583 (19.55%)	7/156 (4.49%)	13/155 (8.39%)
Influenza like illness [A] *	11/583 (1.89%)	0/156 (0%)	0/155 (0%)
Mucosal Inflammation [A] *	67/583 (11.49%)	0/156 (0%)	0/155 (0%)
Non-cardiac chest pain [A] *	23/583 (3.95%)	8/156 (5.13%)	7/155 (4.52%)
Oedema peripheral [A] *	21/583 (3.6%)	0/156 (0%)	0/155 (0%)
Pyrexia [A] *	69/583 (11.84%)	9/156 (5.77%)	10/155 (6.45%)
Infections and infestations			
Paronychia [A] *	30/583 (5.15%)	9/156 (5.77%)	12/155 (7.74%)
Upper respiratory tract infection [A] *	24/583 (4.12%)	0/156 (0%)	0/155 (0%)
Investigations			
Alanine aminotransferase increased [A] *	26/583 (4.46%)	0/156 (0%)	0/155 (0%)
Haemoglobin decreased [A] *	40/583 (6.86%)	0/156 (0%)	0/155 (0%)
Neutrophil count decreased [A] *	19/583 (3.26%)	0/156 (0%)	0/155 (0%)
Platelet count decreased [A] *	40/583 (6.86%)	0/156 (0%)	0/155 (0%)
White blood cell count decreased [A] *	20/583 (3.43%)	0/156 (0%)	0/155 (0%)
Metabolism and nutrition disorders			
Decreased appetite [A] *	112/583 (19.21%)	8/156 (5.13%)	13/155 (8.39%)
Hypokalaemia [A] *	37/583 (6.35%)	0/156 (0%)	0/155 (0%)
Hypomagnesaemia [A] *	69/583 (11.84%)	9/156 (5.77%)	14/155 (9.03%)

	Cetuximab 250 mg/m^2 q1w + Platinum-based Doublet Chemotherapy	Cetuximab 500 mg/ m^2 Every 2 Weeks	Cetuximab 250 mg/m^2 Weekly
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Hyponatraemia [A] *	14/583 (2.4%)	0/156 (0%)	0/155 (0%)
Musculoskeletal and connective tissue disorders			
Arthralgia [A] *	33/583 (5.66%)	5/156 (3.21%)	11/155 (7.1%)
Back pain [A] *	30/583 (5.15%)	6/156 (3.85%)	8/155 (5.16%)
Bone pain [A] *	0/583 (0%)	2/156 (1.28%)	8/155 (5.16%)
Hypercreatinaemia [A] *	5/583 (0.86%)	0/156 (0%)	0/155 (0%)
Musculoskeletal pain [A] *	0/583 (0%)	10/156 (6.41%)	6/155 (3.87%)
Myalgia [A] *	26/583 (4.46%)	0/156 (0%)	0/155 (0%)
Pain in extremity [A] *	31/583 (5.32%)	0/156 (0%)	0/155 (0%)
Nervous system disorders			
Dizziness [A] *	35/583 (6%)	4/156 (2.56%)	8/155 (5.16%)
Dysgeusia [A] *	28/583 (4.8%)	0/156 (0%)	0/155 (0%)
Headache [A] *	29/583 (4.97%)	7/156 (4.49%)	9/155 (5.81%)
Neuropathy peripheral [A] *	26/583 (4.46%)	0/156 (0%)	0/155 (0%)
Peripheral motor neuropathy [A] *	8/583 (1.37%)	0/156 (0%)	0/155 (0%)
Peripheral sensory neuropathy [A] *	38/583 (6.52%)	9/156 (5.77%)	6/155 (3.87%)
Psychiatric disorders			
Insomnia [A] *	31/583 (5.32%)	0/156 (0%)	0/155 (0%)
Respiratory, thoracic and mediastinal disorders			
Cough [A] *	43/583 (7.38%)	20/156 (12.82%)	22/155 (14.19%)
Dysphonia [A] *	17/583 (2.92%)	0/156 (0%)	0/155 (0%)

	Cetuximab 250 mg/m^2 q1w + Platinum-based Doublet Chemotherapy	Cetuximab 500 mg/ m^2 Every 2 Weeks	Cetuximab 250 mg/m^2 Weekly
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Dyspnoea [A] *	69/583 (11.84%)	14/156 (8.97%)	14/155 (9.03%)
Epistaxis [A] *	49/583 (8.4%)	0/156 (0%)	0/155 (0%)
Haemoptysis [A] *	15/583 (2.57%)	0/156 (0%)	0/155 (0%)
Oropharyngeal Pain [A] *	13/583 (2.23%)	0/156 (0%)	0/155 (0%)
Skin and subcutaneous tissue disorders			
Acne [A] *	31/583 (5.32%)	0/156 (0%)	0/155 (0%)
Alopecia [A] *	109/583 (18.7%)	0/156 (0%)	0/155 (0%)
Dermatitis acneiform [A] *	83/583 (14.24%)	11/156 (7.05%)	16/155 (10.32%)
Dry skin [A] *	46/583 (7.89%)	9/156 (5.77%)	11/155 (7.1%)
Nail disorder [A] *	0/583 (0%)	11/156 (7.05%)	13/155 (8.39%)
Pruritus [A] *	51/583 (8.75%)	10/156 (6.41%)	6/155 (3.87%)
Rash [A] *	306/583 (52.49%)	40/156 (25.64%)	40/155 (25.81%)
Rash generalised [A] *	6/583 (1.03%)	0/156 (0%)	0/155 (0%)
Vascular disorders			
Hypertension [A] *	19/583 (3.26%)	0/156 (0%)	0/155 (0%)
Phlebitis [A] *	13/583 (2.23%)	0/156 (0%)	0/155 (0%)

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A Term from vocabulary, MedDRA 14.0

Limitations and Caveats

Enrollment was stopped prematurely when cetuximab did not gain regulatory approval in this indication.

More Information

Certain Agreements:

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

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

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