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

ClinicalTrials.gov ID: NCT00678535

Study Identification

Unique Protocol ID:	EMR 200048-052
Brief Title:	Erbitux in Combination With Xeloda and Cisplatin in Advanced Esophago-gastric Cancer (EXPAND)
Official Title:	Open-label, Randomized, Controlled, Multicenter Phase III Study Investigating Cetuximab in Combination With Capecitabine (Xeloda, X) and Cisplatin (P) Versus XP Alone as First-line Treatment for Subjects With Advanced Gastric Adenocarcinoma Including Adenocarcinoma of the Gastroesophageal Junction
Secondary IDs:	2007-004219-75 [EudraCT Number]

Study Status

Record Verification:	July 2014
Overall Status:	Completed
Study Start:	June 2008
Primary Completion:	March 2012 [Actual]
Study Completion:	February 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: 28/01/2008 Board Name: Comite Independiente de Etica para Ensayos en Farmacología Clínica Board Affiliation: ANMAT - Administración Nacional de Medicamentos, Alimentos y Tecnología Medica Phone: 54-11-4340-0800 / 54-11-5252-82 Email:
Data Monitoring?:	Yes
Plan to Share Data?:	
Oversight Authorities:	Argentina: Administracion Nacional de Medicamentos, Alimentos y Tecnologia Medica Australia: Department of Health and Ageing Therapeutic Goods Administration Australia: Human Research Ethics Committee Austria: Austrian Medicines and Medical Devices Agency Austria: Ethikkommission Belgium: Federal Agency for Medicines and Health Products, FAMHP Belgium: Ethics Committee Brazil: National Committee of Ethics in Research Bulgaria: Bulgarian Drug Agency Bulgaria: Ethics committee Chile: Comité de Ética Científico Chile: Comisión Nacional de Investigación Científica y Tecnológica China: Food and Drug Administration China: Ethics Committee Czech Republic: Ethics Committee Czech Republic: State Institute for Drug Control France: Afssaps - Agence française de sécurité sanitaire des produits de santé (Saint-Denis) France: Agence Nationale de Sécurité du Médicament et des produits de santé Germany: Paul-Ehrlich-Institut Greece: Ethics Committee Greece: National Organization of Medicines Hong Kong: Ethics Committee Israel: Ethics Commission Israel: Israeli Health Ministry Pharmaceutical Administration Italy: National Monitoring Centre for Clinical Trials - Ministry of Health Italy: Ethics Committee Japan: Foundation for Biomedical Research and Innovation Japan: Institutional Review Board Korea: Food and Drug Administration Korea: Institutional Review Board Poland: Ministry of Science and Higher Education

Poland: National Institute of Medicines
Poland: Office for Registration of Medicinal Products, Medical Devices and Biocidal Products
Portugal: Ethics Committee for Clinical Research
Portugal: Health Ethic Committee
Portugal: National Pharmacy and Medicines Institute
Romania: Ethics Committee
Romania: Ministry of Public Health
Romania: National Agency for Medicines and Medical Devices
Romania: National Authority for Scientific Research
Russia: Ethics Committee
Russia: Pharmacological Committee, Ministry of Health
Spain: Agencia Española de Medicamentos y Productos Sanitarios
Spain: Comité Ético de Investigación Clínica
Taiwan : Food and Drug Administration
Taiwan: Institutional Review Board
United Kingdom: Medicines and Healthcare Products Regulatory Agency
United Kingdom: Research Councils UK

Study Description

Brief Summary: The primary objective of this study is to demonstrate that addition of cetuximab to 1st-line treatment with capecitabine (Xeloda, X) and cisplatin (P) [XP] chemotherapy regimen has a clinically relevant benefit for subjects with advanced gastric adenocarcinoma including gastroesophageal junction (GEJ) adenocarcinoma, in terms of progression free survival (PFS).

Secondary objectives are to assess cetuximab plus XP versus XP alone with respect to overall survival, overall tumor response, quality of life (QoL) and safety.

Detailed Description:

Conditions

Conditions: Gastric Cancer

Keywords: 1st line treatment for Gastric Cancer
Cetuximab
Capecitabine
Xeloda
Cisplatin
Progression-free survival

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:	904 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Cetuximab plus Capecitabine plus Cisplatin	Drug: Cetuximab Single first dose of cetuximab 400 milligram per square meter (mg/m^2) will be administered intravenously over 120 minutes followed by weekly intravenous infusion of cetuximab 250 mg/m^2 over 60 minutes in each 3-week treatment cycle, until documented disease progression, unacceptable toxicity, or withdrawal of consent. Other Names: • Erbitux Drug: Capecitabine Capecitabine 1000 mg/m^2 will be administered orally twice daily from evening of Day 1 to morning of Day 15 for every 3-week treatment cycle, until documented disease progression, unacceptable toxicity, or withdrawal of consent. Other Names: • Xeloda Drug: Cisplatin Cisplatin 80 mg/m^2 will be administered intravenously with infusion over 1 to 4 hours on Day 1 of each 3-week treatment cycle, until documented disease progression, unacceptable toxicity, or withdrawal of consent.
Active Comparator: Capecitabine plus Cisplatin	Drug: Capecitabine Capecitabine 1000 mg/m^2 will be administered orally twice daily from evening of Day 1 to morning of Day 15 for every 3-week treatment cycle, until documented disease progression, unacceptable toxicity, or withdrawal of consent. Other Names:

Arms	Assigned Interventions
	• Xeloda Drug: Cisplatin Cisplatin 80 mg/m^2 will be administered intravenously with infusion over 1 to 4 hours on Day 1 of each 3-week treatment cycle, until documented disease progression, unacceptable toxicity, or withdrawal of consent.

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age:

Gender: Both

Accepts Healthy Volunteers?: No

Criteria: Inclusion Criteria:

- Written informed consent before any study-related activities are carried out
- Age greater than or equal to (>=) 18 years
- Histologically confirmed adenocarcinoma of the stomach or gastroesophageal junction (Adenocarcinoma of the gastroesophageal junction [AEG] Types I-III according to Siewert classification)
- Archived tumor material sample for at least subsequent standardized Epidermal Growth Factor Receptor (EGFR) expression assessment
- Unresectable advanced (M0) or unresectable metastatic (M1) disease
- At least one radiographically documented measurable lesion in a previously non-irradiated area according to response evaluation criteria in solid tumors (RECIST). The primary tumor site is to be considered as a non-measurable lesion only
- Eastern Cooperative Oncology Group (ECOG) performance status 0-1
- Estimated life expectancy greater than (>) 12 weeks
- Medically accepted contraception (if the risk of conception exists)
- Glomerular filtration rate (GFR) >= 60 milliliter per minute (mL/min) The GFR is based on the Cockcroft-Gault formula for creatinine clearance
- Aspartate-aminotransferase (ASAT) less than or equal to (=<) 2.5 * upper limit of normal (ULN) and alanine-aminotransferase (ALAT) =< 2.5 *ULN
- Bilirubin =< 3 * ULN
- Absolute neutrophil count (ANC) >= 1.5 * 10^9 per liter
- Platelets >= 100 * 10^9 per liter
- Hemoglobin >=10 gram per deciliter (g/dL) (without transfusions)
- Sodium and potassium within normal limits or =< 10 percent above or below (supplementation permitted)

Exclusion Criteria:

- Prior chemotherapy, however, previous (neo-)adjuvant (radio-) chemotherapy allowed if finished > 1 year prior to start of study treatment and no more than 300 mg/m^2 cisplatin has been administered
- Prior treatment with an antibody or molecule targeting EGFR and/or Vascular Endothelial Growth Factor Receptor (VEGFR) related signaling pathways
- Brain metastasis and/or leptomeningeal disease (known or suspected)
- Radiotherapy (except localized radiotherapy for pain relief), major surgery or any investigational drug within 30 days before the start of study treatment
- Concurrent chronic systemic immune or hormone therapy not indicated in this study protocol (except for physiologic replacement)
- Clinically relevant coronary artery disease (New York Heart Association [NYHA] functional angina classification III/IV), congestive heart failure (NYHA III/IV), clinically relevant cardiomyopathy, history of myocardial infarction in the 12 months before study Screening, or high risk of uncontrolled arrhythmia
- Active Hepatitis B or C
- Chronic diarrhea or short bowel syndrome
- Presence of any contra-indication to treatment with cetuximab, capecitabine and cisplatin including:
    - Known hypersensitivity to capecitabine, fluorouracil, cisplatin, cetuximab or to any of the excipients of these drugs
    - Known dihydropyrimidine dehydrogenase (DPD) deficiency
    - Hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption
    - Current treatment with sorivudine or chemically related analogues, such as brivudine
    - Symptomatic peripheral neuropathy National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grade >= 2 and/or ototoxicity NCI CTCAE Grade >= 2, except if due to trauma or mechanical impairment due to tumor mass
- Pregnancy or lactation period
- Concurrent treatment with a non-permitted drug
- Treatment in another clinical study within 30 days prior to study screening
- Previous malignancy other than gastric cancer within 5 years prior to study screening, except for basal cell cancer of the skin or pre-invasive cancer of the cervix
- Medical or psychological conditions that would not permit the subject to complete the study or sign informed consent
- Legal incapacity or limited legal capacity
- Significant disease which, in the Investigator's opinion, would exclude the subject from the study

Contacts/Locations

Study Officials: Florian Lordick, MD, PhD
Study Principal Investigator
University Clinic Leipzig, University Cancer Center Leipzig (UCCL), Leipzig Germany

Locations: Austria
Research Site
Wien, Austria

Research Site
Zams, Austria

Belgium
Research Site
Bonheiden, Belgium

Research Site
Bruxelles, Belgium

Czech Republic
Research Site
Brno, Czech Republic

Research Site
Hradec Králové, Czech Republic

Germany
Research Site
Berlin, Germany

Research Site
Regensburg, Germany

Research Site
Heidelberg, Germany

Research Site
Schwäbisch Hall, Germany

Research Site
Hamburg, Germany

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München, Germany

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Mainz, Germany

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Weilheim, Germany

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Giessen, Germany

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Essen, Germany

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Dresden, Germany

Research Site
Troisdorf, Germany

Hungary
Research Site
Tatabanya, Hungary

Research Site
Kaposvar, Hungary

Korea, Republic of
Research Site
Seoul, Korea, Republic of

Romania
Research Site
Cluj-Napoca, Romania

Research Site
Bucharest, Romania

Germany
Research Site
Timisoara, Germany

Romania
Research Site
Iasi, Romania

Spain
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Alicante, Spain

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Santander, Spain

Research Site
Valencia, Spain

Taiwan
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Taipei, Taiwan

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Tainan, Taiwan

Austria
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Kufstein, Austria

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Graz, Austria

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Steyr, Austria

Belgium
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Verviers, Belgium

Czech Republic
Research site
Prague 5, Czech Republic

Germany
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Braunschweig, Germany

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Stuttgart, Germany

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Ulm, Germany

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Bielefeld, Germany

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Köln, Germany

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Offenbach, Germany

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Weiden, Germany

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Frankfurt, Germany

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Schweinfurt, Germany

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Ludwigshafen, Germany

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Esslingen, Germany

Hungary
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Gyor, Hungary

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Budapest, Hungary

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Inchon-si, Korea, Republic of

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Seongnam, Korea, Republic of

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Daegu, Korea, Republic of

Romania
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Timisoara, Romania

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Baia-Mare, Romania

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Pamplona, Spain

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Lugo, Spain

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El Palmar-Murcia, Spain

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Seville, Spain

Taiwan
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Changhua, Taiwan

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Rosario, Argentina

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Valparaiso, Chile

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Campinas, Brazil

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Santo André, Brazil

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Ijui, Brazil

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Rousse, Bulgaria

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Sofia, Bulgaria

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Temuco, Chile

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Santiago, Chile

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Reñaca, Chile

China
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Shanghai, China

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Nanjing, China

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Shenyang, China

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Guangzhou, China

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Beijing, China

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Hefei, China

France
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Rennes, France

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Clermont Ferrand Cedex 1, France

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La Roche sur Yon, France

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Paris 14, France

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Besancon, France

Greece
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Ioannina, Greece

Research site
Thessaloniki, Greece

Hong Kong
Research site
Hong Kong, Hong Kong

Israel
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Haifa, Israel

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Tel Aviv, Israel

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Petach Tiqva, Israel

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Ramat Gan, Israel

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Jerusalem, Israel

Italy
Research site
Ancona, Italy

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Milano, Italy

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Rozzano (Milano), Italy

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Bologna, Italy

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Roma, Italy

Japan
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Saitama, Japan

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Tokyo, Japan

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Yokohama, Japan

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Osaka, Japan

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Nagoya, Japan

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Ehime, Japan

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Tochigi, Japan

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Chiba, Japan

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Shizuoka, Japan

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Opole, Poland

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Russian Federation
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Saint-Petersburg, Russian Federation

Research site
Kazan, Russian Federation

Research site
Moscow, Russian Federation

Research site
Obninsk, Russian Federation

United Kingdom
Research site
Manchester, United Kingdom

Research site
Guildford, United Kingdom

Australia
Research site
Coburg VIC, Australia

References

Citations:

Links:

Study Data/Documents:

Study Results

Participant Flow

Recruitment Details	First/last participant (informed consent): June 2008/December 2010. Clinical data cut-off: 31 March 2012 Study completion 17 February 2013.
Pre-Assignment Details	Enrolled: 1,191 screened for eligibility; 287 excluded (mainly non-fulfillment of inclusion or exclusion criteria). 904 participants randomized.

Reporting Groups

	Description
Cetuximab Plus Capecitabine Plus Cisplatin	Cetuximab weekly (initial dose 400 milligram per square meter [mg/m^2] followed by 250 mg/m^2 intravenous infusion), cisplatin (3-week cycle, 80 mg/m^2 intravenous infusion on Day 1) and capecitabine (3-week cycle, 1000 mg/m^2 orally twice daily for 14 days) until documented disease progression, unacceptable toxicity, or withdrawal of consent.
Capecitabine Plus Cisplatin	Cisplatin (3-week cycle, 80 mg/m^2 intravenous infusion on Day 1) and capecitabine (3-week cycle, 1000 mg/m^2 orally twice daily for 14 days) until documented disease progression, unacceptable toxicity, or withdrawal of consent.

Overall Study

	Cetuximab Plus Capecitabine Plus Cisplatin	Capecitabine Plus Cisplatin
Started	455 [1]	449 [1]

	Cetuximab Plus Capecitabine Plus Cisplatin	Capecitabine Plus Cisplatin
Completed	362 [2]	351 [2]
Not Completed	93	98

[1] ITT population
[2] subjects who died before or at 31 March 2012

Baseline Characteristics

Reporting Groups

	Description
Cetuximab Plus Capecitabine Plus Cisplatin	Cetuximab weekly (initial dose 400 milligram per square meter [mg/m^2] followed by 250 mg/m^2 intravenous infusion), cisplatin (3-week cycle, 80 mg/m^2 intravenous infusion on Day 1) and capecitabine (3-week cycle, 1000 mg/m^2 orally twice daily for 14 days) until documented disease progression, unacceptable toxicity, or withdrawal of consent.
Capecitabine Plus Cisplatin	Cisplatin (3-week cycle, 80 mg/m^2 intravenous infusion on Day 1) and capecitabine (3-week cycle, 1000 mg/m^2 orally twice daily for 14 days) until documented disease progression, unacceptable toxicity, or withdrawal of consent.

Baseline Measures

	Cetuximab Plus Capecitabine Plus Cisplatin	Capecitabine Plus Cisplatin	Total
Number of Participants	455	449	904
Age, Continuous [units: years] Mean (Standard Deviation)	58.0 (11.16)	58.5 (10.83)	58.3 (11.00)
Gender, Male/Female [units: participants]			
Female	116	115	231
Male	339	334	673

Outcome Measures

1. Primary Outcome Measure:

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

Measure Description	The PFS time is defined as the duration from randomization to either first observation of progressive disease (PD) or occurrence of death due to any cause within 60 days of the last tumor assessment or randomization. Participants 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 participant randomized, that is, 30 Jun 2008 until cut-off date (31 Mar 2012)
Safety Issue?	No

Analysis Population Description

Intent-to-treat (ITT) population included all participants who were randomized to trial treatment.

Reporting Groups

	Description
Cetuximab Plus Capecitabine Plus Cisplatin	Cetuximab weekly (initial dose 400 milligram per square meter [mg/m^2] followed by 250 mg/m^2 intravenous infusion), cisplatin (3-week cycle, 80 mg/m^2 intravenous infusion on Day 1) and capecitabine (3-week cycle, 1000 mg/m^2 orally twice daily for 14 days) until documented disease progression, unacceptable toxicity, or withdrawal of consent.
Capecitabine Plus Cisplatin	Cisplatin (3-week cycle, 80 mg/m^2 intravenous infusion on Day 1) and capecitabine (3-week cycle, 1000 mg/m^2 orally twice daily for 14 days) until documented disease progression, unacceptable toxicity, or withdrawal of consent.

Measured Values

	Cetuximab Plus Capecitabine Plus Cisplatin	Capecitabine Plus Cisplatin
Number of Participants Analyzed	455	449
Progression-free Survival (PFS) Time: Independent Review Committee (IRC) Assessments [units: months] Median (95% Confidence Interval)	4.4 (4.2 to 5.5)	5.6 (5.1 to 5.7)

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

Statistical Analysis Overview	Comparison Groups	Cetuximab Plus Capecitabine Plus Cisplatin, Capecitabine Plus Cisplatin
	Comments	Primary efficacy analysis: To test equality of progression free survival time between treatment groups, applying the two-sided stratified log-rank test (randomization strata: disease stage, previous oesophagectomy/gastrectomy and prior(neo−) adjuvant(radio) chemotherapy, α=5%).
	Non-Inferiority or Equivalence Analysis?	No

	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.3158
	Comments	[Not specified]
	Method	Other [Stratified log rank]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	1.091
	Confidence Interval	(2-Sided) 95% 0.920 to 1.292
	Estimation Comments	Kaplan-Meier method was used to estimate median PFS time. HR was calculated using Cox proportional hazards model stratified by randomization strata.

2. Secondary Outcome Measure:

Measure Title	Overall Survival (OS)
Measure Description	The OS time is defined as the time from randomization to death or last day known to be alive. Participants 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 participant randomized, that is, 30 Jun 2008 until cut-off date, (31 Mar 2012)
Safety Issue?	No

Analysis Population Description

ITT population included all participants who were randomized to trial treatment.

Reporting Groups

	Description
Cetuximab Plus Capecitabine Plus Cisplatin	Cetuximab weekly (initial dose 400 milligram per square meter [mg/m^2] followed by 250 mg/m^2 intravenous infusion), cisplatin (3-week cycle, 80 mg/m^2 intravenous infusion on Day 1) and capecitabine (3-week cycle, 1000 mg/m^2 orally twice daily for 14 days) until documented disease progression, unacceptable toxicity, or withdrawal of consent.
Capecitabine Plus Cisplatin	Cisplatin (3-week cycle, 80 mg/m^2 intravenous infusion on Day 1) and capecitabine (3-week cycle, 1000 mg/m^2 orally twice daily for 14 days) until documented disease progression, unacceptable toxicity, or withdrawal of consent.

Measured Values

	Cetuximab Plus Capecitabine Plus Cisplatin	Capecitabine Plus Cisplatin
Number of Participants Analyzed	455	449
Overall Survival (OS) [units: months] Median (95% Confidence Interval)	9.4 (8.3 to 10.6)	10.7 (9.4 to 11.3)

Statistical Analysis 1 for Overall Survival (OS)

Statistical Analysis Overview	Comparison Groups	Cetuximab Plus Capecitabine Plus Cisplatin, Capecitabine Plus Cisplatin
	Comments	To test equality of OS time between treatment groups, applying the two-sided stratified log-rank test (randomization strata: disease stage, previous oesophagectomy/gastrectomy and prior (neo−) adjuvant(radio) chemotherapy, α=5%)
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.9547
	Comments	[Not specified]
	Method	Other [Stratified log rank]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	1.004
	Confidence Interval	(2-Sided) 95% 0.866 to 1.165
	Estimation Comments	Kaplan-Meier method was used to estimate median OS time. HR was calculated using Cox proportional hazards model stratified by randomization strata.

3. Secondary Outcome Measure:

Measure Title	Best Overall Response (BOR) Rate: Independent Review Committee (IRC) Assessments
Measure Description	The BOR rate is defined as the percentage of participants having achieved complete response (CR) or partial response (PR) as the best overall response, based on radiological assessments (based on response evaluation criteria in solid tumors [RECIST] Version 1.0) from the IRC.

Time Frame	Every 6 weeks until progression, reported between day of first participant randomized, that is, 30 Jun 2008 until cut-off date, (31 Mar 2012)
Safety Issue?	No

Analysis Population Description

ITT population included all participants who were randomized to trial treatment.

Reporting Groups

	Description
Cetuximab Plus Capecitabine Plus Cisplatin	Cetuximab weekly (initial dose 400 milligram per square meter [mg/m^2] followed by 250 mg/m^2 intravenous infusion), cisplatin (3-week cycle, 80 mg/m^2 intravenous infusion on Day 1) and capecitabine (3-week cycle, 1000 mg/m^2 orally twice daily for 14 days) until documented disease progression, unacceptable toxicity, or withdrawal of consent.
Capecitabine Plus Cisplatin	Cisplatin (3-week cycle, 80 mg/m^2 intravenous infusion on Day 1) and capecitabine (3-week cycle, 1000 mg/m^2 orally twice daily for 14 days) until documented disease progression, unacceptable toxicity, or withdrawal of consent.

Measured Values

	Cetuximab Plus Capecitabine Plus Cisplatin	Capecitabine Plus Cisplatin
Number of Participants Analyzed	455	449
Best Overall Response (BOR) Rate: Independent Review Committee (IRC) Assessments [units: percentage of participants] Number (95% Confidence Interval)	29.9 (25.7 to 34.3)	29.2 (25.0 to 33.6)

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

Statistical Analysis Overview	Comparison Groups	Cetuximab Plus Capecitabine Plus Cisplatin, Capecitabine Plus Cisplatin
	Comments	The best overall response rate was compared with the Cochran-Mantel-Haenszel test (strata: disease stage, previous oesophagectomy/gastrectomy and prior(neo−) adjuvant(radio) chemotherapy, two-sided with α=5%).
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.7696
	Comments	[Not specified]

	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	1.0435
	Confidence Interval	(2-Sided) 95% 0.7844 to 1.3882
	Estimation Comments	[Not specified]

4. Secondary Outcome Measure:

Measure Title	Quality of Life (QoL) Assessed by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)
Measure Description	Mean global health status and 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 better QoL.
Time Frame	Baseline, Week 6, 12, 18, 24, 30, 36, 42, 48, 54 and 60, reported between day of first participant randomized, that is, 30 Jun 2008 until cut-off date (31 Mar 2012)
Safety Issue?	No

Analysis Population Description

Analysis population included participants who had at least one evaluable EORTC QLQ-C30 questionnaire and were also included in the ITT population. 'N' (number of participants analyzed) signifies participants who were evaluable for this measure.

Reporting Groups

	Description
Cetuximab Plus Capecitabine Plus Cisplatin	Cetuximab weekly (initial dose 400 milligram per square meter [mg/m^2] followed by 250 mg/m^2 intravenous infusion), cisplatin (3-week cycle, 80 mg/m^2 intravenous infusion on Day 1) and capecitabine (3-week cycle, 1000 mg/m^2 orally twice daily for 14 days) until documented disease progression, unacceptable toxicity, or withdrawal of consent.
Capecitabine Plus Cisplatin	Cisplatin (3-week cycle, 80 mg/m^2 intravenous infusion on Day 1) and capecitabine (3-week cycle, 1000 mg/m^2 orally twice daily for 14 days) until documented disease progression, unacceptable toxicity, or withdrawal of consent.

Measured Values

	Cetuximab Plus Capecitabine Plus Cisplatin	Capecitabine Plus Cisplatin
Number of Participants Analyzed	450	430

	Cetuximab Plus Capecitabine Plus Cisplatin	Capecitabine Plus Cisplatin
Quality of Life (QoL) Assessed by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) [units: units on a scale] Mean (Standard Deviation)		
Global health status: Baseline	57.49 (22.168)	57.19 (22.124)
Global health status: Week 6	59.00 (21.879)	61.80 (22.089)
Global health status: Week 12	60.17 (20.796)	63.35 (22.077)
Global health status: Week 18	60.45 (20.015)	61.83 (21.499)
Global health status: Week 24	62.46 (22.978)	63.61 (19.477)
Global health status: Week 30	63.65 (21.722)	64.11 (19.757)
Global health status: Week 36	65.06 (22.629)	57.72 (21.602)
Global health status: Week 42	59.29 (21.558)	62.64 (22.005)
Global health status: Week 48	63.39 (21.317)	66.67 (19.395)
Global health status: Week 54	60.63 (16.198)	66.67 (14.651)
Global health status: Week 60	62.50 (13.918)	61.81 (17.210)
Social functioning status: Baseline	74.36 (27.077)	76.52 (26.601)
Social functioning status: Week 6	68.94 (28.885)	75.70 (27.415)
Social functioning status: Week 12	71.48 (26.547)	75.65 (27.691)
Social functioning status: Week 18	71.22 (25.317)	75.51 (25.612)
Social functioning status: Week 24	74.20 (26.143)	78.26 (27.633)
Social functioning status: Week 30	78.51 (24.766)	76.67 (24.962)
Social functioning status: Week 36	76.28 (21.730)	73.58 (22.353)
Social functioning status: Week 42	68.57 (27.348)	78.16 (22.318)
Social functioning status at Week 48	80.36 (22.705)	78.00 (23.432)
Social functioning status: Week 54	74.71 (27.682)	80.56 (27.371)
Social functioning status: Week 60	78.33 (23.632)	68.06 (32.144)

5. Secondary Outcome Measure:

Measure Title	Quality of Life (QoL) Assessed by EuroQol 5Dimensions (EQ-5D) Questionnaire
Measure Description	EQ-5D questionnaire is a measure of health status that provides a simple descriptive profile and a single index value. The EQ-5D defines health in terms of mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The 5 single items are combined to obtain a single index score that is health utility index (HUI) score reflecting subject's preferences for different health states. The lowest possible score is -0.59 and the highest is 1.00, higher scores on the EQ-5D represent a better QoL.
Time Frame	Baseline, Week 6, 12, 18, 24, 30, 36, 42, 48, 54 and 60, reported between day of first participant randomized, that is, 30 Jun 2008 until cut-off date (31 Mar 2012)
Safety Issue?	No

Analysis Population Description

Analysis population included participants who had at least one evaluable EuroQoL EQ-5D questionnaire and were also included in the ITT population. 'N' (number of participants analyzed) signifies participants who were evaluable for this measure.

Reporting Groups

	Description
Cetuximab Plus Capecitabine Plus Cisplatin	Cetuximab weekly (initial dose 400 milligram per square meter [mg/m^2] followed by 250 mg/m^2 intravenous infusion), cisplatin (3-week cycle, 80 mg/m^2 intravenous infusion on Day 1) and capecitabine (3-week cycle, 1000 mg/m^2 orally twice daily for 14 days) until documented disease progression, unacceptable toxicity, or withdrawal of consent.
Capecitabine Plus Cisplatin	Cisplatin (3-week cycle, 80 mg/m^2 intravenous infusion on Day 1) and capecitabine (3-week cycle, 1000 mg/m^2 orally twice daily for 14 days) until documented disease progression, unacceptable toxicity, or withdrawal of consent.

Measured Values

	Cetuximab Plus Capecitabine Plus Cisplatin	Capecitabine Plus Cisplatin
Number of Participants Analyzed	450	430
Quality of Life (QoL) Assessed by EuroQol 5Dimensions (EQ-5D) Questionnaire [units: units on a scale] Mean (Standard Deviation)		
Baseline	0.743 (0.240)	0.749 (0.235)
Week 6	0.739 (0.276)	0.769 (0.254)
Week 12	0.752 (0.239)	0.775 (0.246)

	Cetuximab Plus Capecitabine Plus Cisplatin	Capecitabine Plus Cisplatin
Week 18	0.742 (0.251)	0.755 (0.235)
Week 24	0.733 (0.300)	0.761 (0.265)
Week 30	0.737 (0.301)	0.790 (0.230)
Week 36	0.710 (0.311)	0.711 (0.309)
Week 42	0.722 (0.209)	0.689 (0.307)
Week 48	0.719 (0.227)	0.770 (0.216)
Week 54	0.733 (0.275)	0.730 (0.191)
Week 60	0.760 (0.322)	0.742 (0.170)

6. Secondary Outcome Measure:

Measure Title	Safety - Number of Participants With Adverse Events (AEs)
Measure Description	An Adverse Event (AE) is defined as any untoward medical occurrence in the form of signs, symptoms, abnormal laboratory findings, or diseases that emerges or worsens relative to Baseline during a clinical study with an investigational medicinal product (IMP), regardless of causal relationship and even if no IMP has been administered.
Time Frame	Time from first dose up to Day 30 after last dose of study treatment, reported between day of first participant randomized, that is, 30 Jun 2008 until cut-off date (31 Mar 2012)
Safety Issue?	Yes

Analysis Population Description

The safety population included all participants who received at least one dose of any trial treatment that is, cetuximab, cisplatin, or capecitabine.

Reporting Groups

	Description
Cetuximab Plus Capecitabine Plus Cisplatin	Cetuximab weekly (initial dose 400 milligram per square meter [mg/m^2] followed by 250 mg/m^2 intravenous infusion), cisplatin (3-week cycle, 80 mg/m^2 intravenous infusion on Day 1) and capecitabine (3-week cycle, 1000 mg/m^2 orally twice daily for 14 days) until documented disease progression, unacceptable toxicity, or withdrawal of consent.
Capecitabine Plus Cisplatin	Cisplatin (3-week cycle, 80 mg/m^2 intravenous infusion on Day 1) and capecitabine (3-week cycle, 1000 mg/m^2 orally twice daily for 14 days) until documented disease progression, unacceptable toxicity, or withdrawal of consent.

Measured Values

	Cetuximab Plus Capecitabine Plus Cisplatin	Capecitabine Plus Cisplatin
Number of Participants Analyzed	446	436
Safety - Number of Participants With Adverse Events (AEs) [units: participants]	446	432

Reported Adverse Events

Time Frame	Time from first dose up to 30 days after the last dose of study treatment.
Additional Description	An AE is defined as any untoward medical occurrence in the form of signs, symptoms, abnormal laboratory findings, or diseases that emerges or worsens relative to Baseline during a clinical study with an IMP, regardless of causal relationship and even if no IMP has been administered.

Reporting Groups

	Description
Cetuximab Plus Capecitabine Plus Cisplatin	Cetuximab weekly (initial dose 400 milligram per square meter [mg/m^2] followed by 250 mg/m^2 intravenous infusion), cisplatin (3-week cycle, 80 mg/m^2 intravenous infusion on Day 1) and capecitabine (3-week cycle, 1000 mg/m^2 orally twice daily for 14 days) until documented disease progression, unacceptable toxicity, or withdrawal of consent.
Capecitabine Plus Cisplatin	Cisplatin (3-week cycle, 80 mg/m^2 intravenous infusion on Day 1) and capecitabine (3-week cycle, 1000 mg/m^2 orally twice daily for 14 days) until documented disease progression, unacceptable toxicity, or withdrawal of consent.

Serious Adverse Events

	Cetuximab Plus Capecitabine Plus Cisplatin	Capecitabine Plus Cisplatin
	Affected/At Risk (%)	Affected/At Risk (%)
Total	239/446 (53.59%)	194/436 (44.5%)
Blood and lymphatic system disorders		
Anaemia	10/446 (2.24%)	17/436 (3.9%)
Disseminated intravascular coagulation	1/446 (0.22%)	0/436 (0%)
Febrile neutropenia	5/446 (1.12%)	5/436 (1.15%)

	Cetuximab Plus Capecitabine Plus Cisplatin	Capecitabine Plus Cisplatin
	Affected/At Risk (%)	Affected/At Risk (%)
Granulocytopenia	0/446 (0%)	1/436 (0.23%)
Leukopenia	3/446 (0.67%)	7/436 (1.61%)
Neutropenia	9/446 (2.02%)	13/436 (2.98%)
Thrombocytopenia	2/446 (0.45%)	6/436 (1.38%)
Cardiac disorders		
Acute coronary syndrome	1/446 (0.22%)	0/436 (0%)
Acute myocardial infarction	4/446 (0.9%)	2/436 (0.46%)
Angina pectoris	1/446 (0.22%)	0/436 (0%)
Atrial fibrillation	2/446 (0.45%)	2/436 (0.46%)
Atrial flutter	1/446 (0.22%)	0/436 (0%)
Cardiac arrest	3/446 (0.67%)	1/436 (0.23%)
Cardiac failure	1/446 (0.22%)	0/436 (0%)
Cardio-respiratory arrest	2/446 (0.45%)	4/436 (0.92%)
Cardiomyopathy	0/446 (0%)	1/436 (0.23%)
Cardiopulmonary failure	1/446 (0.22%)	1/436 (0.23%)
Intracardiac thrombus	1/446 (0.22%)	1/436 (0.23%)
Myocardial infarction	3/446 (0.67%)	2/436 (0.46%)
Myocardial ischaemia	2/446 (0.45%)	3/436 (0.69%)
Sick sinus syndrome	1/446 (0.22%)	0/436 (0%)
Sinus tachycardia	0/446 (0%)	1/436 (0.23%)
Tachycardia	1/446 (0.22%)	0/436 (0%)
Ventricular extrasystoles	1/446 (0.22%)	0/436 (0%)
Congenital, familial and genetic disorders		
Pyloric stenosis	1/446 (0.22%)	0/436 (0%)
Ear and labyrinth disorders		
Auricular perichondritis	1/446 (0.22%)	0/436 (0%)

	Cetuximab Plus Capecitabine Plus Cisplatin	Capecitabine Plus Cisplatin
	Affected/At Risk (%)	Affected/At Risk (%)
Vertigo	1/446 (0.22%)	1/436 (0.23%)
Endocrine disorders		
Adrenal insufficiency	0/446 (0%)	1/436 (0.23%)
Hyperthyroidism	0/446 (0%)	1/436 (0.23%)
Eye disorders		
Ocular icterus	0/446 (0%)	1/436 (0.23%)
Gastrointestinal disorders		
Abdominal distension	1/446 (0.22%)	0/436 (0%)
Abdominal pain	9/446 (2.02%)	6/436 (1.38%)
Abdominal pain lower	1/446 (0.22%)	1/436 (0.23%)
Abdominal pain upper	3/446 (0.67%)	2/436 (0.46%)
Ascites	9/446 (2.02%)	3/436 (0.69%)
Colonic polyp	0/446 (0%)	1/436 (0.23%)
Constipation	1/446 (0.22%)	5/436 (1.15%)
Diarrhoea	15/446 (3.36%)	15/436 (3.44%)
Dysphagia	6/446 (1.35%)	3/436 (0.69%)
Erosive oesophagitis	0/446 (0%)	1/436 (0.23%)
Gastric haemorrhage	0/446 (0%)	2/436 (0.46%)
Gastric perforation	1/446 (0.22%)	1/436 (0.23%)
Gastric stenosis	1/446 (0.22%)	0/436 (0%)
Gastrointestinal haemorrhage	0/446 (0%)	2/436 (0.46%)
Gastrointestinal obstruction	1/446 (0.22%)	0/436 (0%)
Gastrointestinal stenosis	0/446 (0%)	2/436 (0.46%)
Haematemesis	0/446 (0%)	1/436 (0.23%)
Haemorrhoids	0/446 (0%)	1/436 (0.23%)
Ileus	4/446 (0.9%)	7/436 (1.61%)

	Cetuximab Plus Capecitabine Plus Cisplatin	Capecitabine Plus Cisplatin
	Affected/At Risk (%)	Affected/At Risk (%)
Ileus paralytic	0/446 (0%)	1/436 (0.23%)
Inguinal hernia	0/446 (0%)	1/436 (0.23%)
Intestinal obstruction	3/446 (0.67%)	3/436 (0.69%)
Intestinal perforation	1/446 (0.22%)	1/436 (0.23%)
Mechanical ileus	0/446 (0%)	1/436 (0.23%)
Melaena	2/446 (0.45%)	1/436 (0.23%)
Nausea	11/446 (2.47%)	13/436 (2.98%)
Obstruction gastric	3/446 (0.67%)	2/436 (0.46%)
Oesophageal perforation	1/446 (0.22%)	0/436 (0%)
Pneumatosis intestinalis	1/446 (0.22%)	1/436 (0.23%)
Small intestinal obstruction	0/446 (0%)	1/436 (0.23%)
Stomatitis	0/446 (0%)	1/436 (0.23%)
Subileus	3/446 (0.67%)	1/436 (0.23%)
Upper gastrointestinal haemorrhage	2/446 (0.45%)	2/436 (0.46%)
Vomiting	16/446 (3.59%)	25/436 (5.73%)
General disorders		
Asthenia	6/446 (1.35%)	5/436 (1.15%)
Chest discomfort	0/446 (0%)	1/436 (0.23%)
Death	0/446 (0%)	2/436 (0.46%)
Device dislocation	2/446 (0.45%)	2/436 (0.46%)
Device occlusion	1/446 (0.22%)	0/436 (0%)
Disease progression	7/446 (1.57%)	1/436 (0.23%)
Fatigue	11/446 (2.47%)	5/436 (1.15%)
General physical health deterioration	12/446 (2.69%)	13/436 (2.98%)
Mucosal inflammation	3/446 (0.67%)	3/436 (0.69%)
Multi-organ failure	0/446 (0%)	4/436 (0.92%)

	Cetuximab Plus Capecitabine Plus Cisplatin	Capecitabine Plus Cisplatin
	Affected/At Risk (%)	Affected/At Risk (%)
Non-cardiac chest pain	2/446 (0.45%)	0/436 (0%)
Oedema peripheral	2/446 (0.45%)	0/436 (0%)
Pain	0/446 (0%)	1/436 (0.23%)
Performance status decreased	3/446 (0.67%)	3/436 (0.69%)
Pyrexia	8/446 (1.79%)	7/436 (1.61%)
Stent malfunction	1/446 (0.22%)	0/436 (0%)
Sudden death	1/446 (0.22%)	0/436 (0%)
Hepatobiliary disorders		
Bile duct stenosis	2/446 (0.45%)	0/436 (0%)
Cholecystitis	1/446 (0.22%)	1/436 (0.23%)
Cytolytic hepatitis	1/446 (0.22%)	0/436 (0%)
Hepatic failure	1/446 (0.22%)	0/436 (0%)
Hepatic lesion	0/446 (0%)	1/436 (0.23%)
Hepatotoxicity	1/446 (0.22%)	0/436 (0%)
Hyperbilirubinaemia	1/446 (0.22%)	0/436 (0%)
Jaundice	1/446 (0.22%)	1/436 (0.23%)
Jaundice cholestatic	3/446 (0.67%)	1/436 (0.23%)
Immune system disorders		
Anaphylactic shock	1/446 (0.22%)	0/436 (0%)
Hypersensitivity	4/446 (0.9%)	0/436 (0%)
Infections and infestations		
Abdominal abscess	1/446 (0.22%)	0/436 (0%)
Bacteraemia	1/446 (0.22%)	0/436 (0%)
Bronchitis	0/446 (0%)	1/436 (0.23%)
Bronchopulmonary aspergillosis	1/446 (0.22%)	0/436 (0%)
Candida sepsis	1/446 (0.22%)	0/436 (0%)

	Cetuximab Plus Capecitabine Plus Cisplatin	Capecitabine Plus Cisplatin
	Affected/At Risk (%)	Affected/At Risk (%)
Cellulitis	1/446 (0.22%)	0/436 (0%)
Cystitis	0/446 (0%)	1/436 (0.23%)
Device related infection	3/446 (0.67%)	4/436 (0.92%)
Enterocolitis bacterial	1/446 (0.22%)	0/436 (0%)
Enterocolitis infectious	1/446 (0.22%)	0/436 (0%)
Gangrene	0/446 (0%)	1/436 (0.23%)
Gastroenteritis	3/446 (0.67%)	0/436 (0%)
Herpes zoster	1/446 (0.22%)	0/436 (0%)
Infection	1/446 (0.22%)	0/436 (0%)
Influenza	0/446 (0%)	1/436 (0.23%)
Klebsiella sepsis	1/446 (0.22%)	0/436 (0%)
Liver abscess	1/446 (0.22%)	0/436 (0%)
Oesophageal candidiasis	0/446 (0%)	1/436 (0.23%)
Paronychia	2/446 (0.45%)	0/436 (0%)
Pneumonia	4/446 (0.9%)	8/436 (1.83%)
Pneumonia bacterial	1/446 (0.22%)	0/436 (0%)
Respiratory tract infection	1/446 (0.22%)	0/436 (0%)
Sepsis	5/446 (1.12%)	2/436 (0.46%)
Septic shock	3/446 (0.67%)	0/436 (0%)
Skin infection	1/446 (0.22%)	0/436 (0%)
Upper respiratory tract infection	1/446 (0.22%)	1/436 (0.23%)
Injury, poisoning and procedural complications		
Anastomotic stenosis	1/446 (0.22%)	0/436 (0%)
Concussion	0/446 (0%)	1/436 (0.23%)
Fall	0/446 (0%)	1/436 (0.23%)
Femur fracture	1/446 (0.22%)	0/436 (0%)

	Cetuximab Plus Capecitabine Plus Cisplatin	Capecitabine Plus Cisplatin
	Affected/At Risk (%)	Affected/At Risk (%)
Gastrointestinal stoma complication	1/446 (0.22%)	0/436 (0%)
Infusion related reaction	2/446 (0.45%)	0/436 (0%)
Laceration	0/446 (0%)	1/436 (0.23%)
Overdose	0/446 (0%)	2/436 (0.46%)
Pneumothorax traumatic	0/446 (0%)	1/436 (0.23%)
Post procedural discharge	0/446 (0%)	1/436 (0.23%)
Road traffic accident	0/446 (0%)	1/436 (0.23%)
Upper limb fracture	1/446 (0.22%)	0/436 (0%)
Investigations		
Alanine aminotransferase increased	1/446 (0.22%)	1/436 (0.23%)
Aspartate aminotransferase increased	0/446 (0%)	1/436 (0.23%)
Blood bilirubin increased	2/446 (0.45%)	0/436 (0%)
Blood creatinine increased	1/446 (0.22%)	5/436 (1.15%)
Blood urine	1/446 (0.22%)	0/436 (0%)
Electrocardiogram QT prolonged	2/446 (0.45%)	0/436 (0%)
Electrocardiogram low voltage	1/446 (0.22%)	0/436 (0%)
Glomerular filtration rate decreased	1/446 (0.22%)	0/436 (0%)
International normalised ratio increased	1/446 (0.22%)	0/436 (0%)
Liver function test abnormal	1/446 (0.22%)	0/436 (0%)
Platelet count decreased	0/446 (0%)	1/436 (0.23%)
Prothrombin time prolonged	0/446 (0%)	1/436 (0.23%)
Troponin I increased	0/446 (0%)	2/436 (0.46%)
Troponin increased	1/446 (0.22%)	0/436 (0%)
Weight decreased	2/446 (0.45%)	1/436 (0.23%)
Metabolism and nutrition disorders		
Cachexia	2/446 (0.45%)	0/436 (0%)

	Cetuximab Plus Capecitabine Plus Cisplatin	Capecitabine Plus Cisplatin
	Affected/At Risk (%)	Affected/At Risk (%)
Decreased appetite	15/446 (3.36%)	3/436 (0.69%)
Dehydration	9/446 (2.02%)	15/436 (3.44%)
Diabetes mellitus	1/446 (0.22%)	0/436 (0%)
Electrolyte imbalance	1/446 (0.22%)	0/436 (0%)
Hyperglycaemia	0/446 (0%)	4/436 (0.92%)
Hyperkalaemia	0/446 (0%)	1/436 (0.23%)
Hypocalcaemia	2/446 (0.45%)	2/436 (0.46%)
Hypoglycaemia	0/446 (0%)	1/436 (0.23%)
Hypokalaemia	7/446 (1.57%)	9/436 (2.06%)
Hypomagnesaemia	2/446 (0.45%)	1/436 (0.23%)
Hyponatraemia	2/446 (0.45%)	3/436 (0.69%)
Hypophagia	3/446 (0.67%)	1/436 (0.23%)
Malnutrition	1/446 (0.22%)	0/436 (0%)
Musculoskeletal and connective tissue disorders		
Arthralgia	1/446 (0.22%)	0/436 (0%)
Back pain	1/446 (0.22%)	0/436 (0%)
Bone pain	1/446 (0.22%)	1/436 (0.23%)
Muscular weakness	1/446 (0.22%)	0/436 (0%)
Musculoskeletal chest pain	0/446 (0%)	1/436 (0.23%)
Musculoskeletal pain	1/446 (0.22%)	0/436 (0%)
Soft tissue necrosis	1/446 (0.22%)	0/436 (0%)
Spondylitis	1/446 (0.22%)	0/436 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Metastases to central nervous system	0/446 (0%)	1/436 (0.23%)
Metastases to meninges	0/446 (0%)	1/436 (0.23%)
Metastases to ovary	1/446 (0.22%)	0/436 (0%)

	Cetuximab Plus Capecitabine Plus Cisplatin	Capecitabine Plus Cisplatin
	Affected/At Risk (%)	Affected/At Risk (%)
Neoplasm malignant	1/446 (0.22%)	0/436 (0%)
Tumour associated fever	0/446 (0%)	1/436 (0.23%)
Tumour haemorrhage	3/446 (0.67%)	1/436 (0.23%)
Tumour pain	1/446 (0.22%)	2/436 (0.46%)
Tumour perforation	1/446 (0.22%)	1/436 (0.23%)
Tumour rupture	1/446 (0.22%)	0/436 (0%)
Nervous system disorders		
Brain stem infarction	1/446 (0.22%)	0/436 (0%)
Cerebral haemorrhage	1/446 (0.22%)	2/436 (0.46%)
Cerebral infarction	5/446 (1.12%)	1/436 (0.23%)
Cerebral ischaemia	1/446 (0.22%)	0/436 (0%)
Cerebrovascular accident	0/446 (0%)	1/436 (0.23%)
Convulsion	0/446 (0%)	1/436 (0.23%)
Depressed level of consciousness	0/446 (0%)	1/436 (0.23%)
Dizziness	1/446 (0.22%)	5/436 (1.15%)
Facial paresis	0/446 (0%)	1/436 (0.23%)
Headache	1/446 (0.22%)	1/436 (0.23%)
Hemiparesis	0/446 (0%)	1/436 (0.23%)
Hepatic encephalopathy	1/446 (0.22%)	0/436 (0%)
Ischaemic stroke	3/446 (0.67%)	1/436 (0.23%)
Lumbar radiculopathy	1/446 (0.22%)	0/436 (0%)
Paraesthesia	0/446 (0%)	2/436 (0.46%)
Presyncope	0/446 (0%)	1/436 (0.23%)
Spinal cord compression	1/446 (0.22%)	1/436 (0.23%)
Subarachnoid haemorrhage	0/446 (0%)	1/436 (0.23%)
Syncope	6/446 (1.35%)	4/436 (0.92%)

	Cetuximab Plus Capecitabine Plus Cisplatin	Capecitabine Plus Cisplatin
	Affected/At Risk (%)	Affected/At Risk (%)
Psychiatric disorders		
Completed suicide	0/446 (0%)	2/436 (0.46%)
Delirium	1/446 (0.22%)	0/436 (0%)
Depression	1/446 (0.22%)	0/436 (0%)
Renal and urinary disorders		
Acute prerenal failure	1/446 (0.22%)	2/436 (0.46%)
Calculus ureteric	1/446 (0.22%)	0/436 (0%)
Haematuria	1/446 (0.22%)	0/436 (0%)
Hydronephrosis	1/446 (0.22%)	1/436 (0.23%)
Oliguria	0/446 (0%)	1/436 (0.23%)
Renal colic	1/446 (0.22%)	0/436 (0%)
Renal failure	3/446 (0.67%)	4/436 (0.92%)
Renal failure acute	2/446 (0.45%)	0/436 (0%)
Renal impairment	1/446 (0.22%)	0/436 (0%)
Ureteric obstruction	1/446 (0.22%)	0/436 (0%)
Urinary retention	1/446 (0.22%)	1/436 (0.23%)
Urinary tract obstruction	0/446 (0%)	1/436 (0.23%)
Reproductive system and breast disorders		
Benign prostatic hyperplasia	0/446 (0%)	1/436 (0.23%)
Respiratory, thoracic and mediastinal disorders		
Bronchospasm	1/446 (0.22%)	0/436 (0%)
Dyspnoea	7/446 (1.57%)	4/436 (0.92%)
Pleural effusion	4/446 (0.9%)	1/436 (0.23%)
Pneumonitis	1/446 (0.22%)	0/436 (0%)
Pneumothorax	1/446 (0.22%)	0/436 (0%)
Pulmonary artery thrombosis	1/446 (0.22%)	0/436 (0%)

	Cetuximab Plus Capecitabine Plus Cisplatin	Capecitabine Plus Cisplatin
	Affected/At Risk (%)	Affected/At Risk (%)
Pulmonary embolism	26/446 (5.83%)	13/436 (2.98%)
Pulmonary thrombosis	0/446 (0%)	1/436 (0.23%)
Respiratory failure	1/446 (0.22%)	0/436 (0%)
Skin and subcutaneous tissue disorders		
Dermatitis	1/446 (0.22%)	0/436 (0%)
Dermatitis acneiform	1/446 (0.22%)	0/436 (0%)
Dry skin	1/446 (0.22%)	0/436 (0%)
Palmar-plantar erythrodysaesthesia syndrome	1/446 (0.22%)	0/436 (0%)
Rash	1/446 (0.22%)	0/436 (0%)
Rash generalised	1/446 (0.22%)	0/436 (0%)
Skin disorder	1/446 (0.22%)	0/436 (0%)
Skin exfoliation	1/446 (0.22%)	0/436 (0%)
Skin toxicity	1/446 (0.22%)	0/436 (0%)
Vascular disorders		
Circulatory collapse	0/446 (0%)	1/436 (0.23%)
Deep vein thrombosis	11/446 (2.47%)	2/436 (0.46%)
Hypotension	2/446 (0.45%)	2/436 (0.46%)
Peripheral ischaemia	2/446 (0.45%)	0/436 (0%)
Subclavian vein thrombosis	0/446 (0%)	2/436 (0.46%)
Venous thrombosis	0/446 (0%)	1/436 (0.23%)
Venous thrombosis limb	0/446 (0%)	1/436 (0.23%)

Other Adverse Events

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

	Cetuximab Plus Capecitabine Plus Cisplatin	Capecitabine Plus Cisplatin
	Affected/At Risk (%)	Affected/At Risk (%)
Total	441/446 (98.88%)	429/436 (98.39%)
Blood and lymphatic system disorders		
Anaemia	127/446 (28.48%)	155/436 (35.55%)
Leukopenia	67/446 (15.02%)	94/436 (21.56%)
Neutropenia	194/446 (43.5%)	234/436 (53.67%)
Thrombocytopenia	81/446 (18.16%)	89/436 (20.41%)
Ear and labyrinth disorders		
Tinnitus	20/446 (4.48%)	23/436 (5.28%)
Gastrointestinal disorders		
Abdominal pain	92/446 (20.63%)	72/436 (16.51%)
Abdominal pain upper	67/446 (15.02%)	44/436 (10.09%)
Constipation	120/446 (26.91%)	110/436 (25.23%)
Diarrhoea	172/446 (38.57%)	105/436 (24.08%)
Dyspepsia	45/446 (10.09%)	21/436 (4.82%)
Dysphagia	23/446 (5.16%)	14/436 (3.21%)
Nausea	273/446 (61.21%)	265/436 (60.78%)
Stomatitis	100/446 (22.42%)	41/436 (9.4%)
Vomiting	165/446 (37%)	192/436 (44.04%)
General disorders		
Asthenia	92/446 (20.63%)	98/436 (22.48%)
Fatigue	187/446 (41.93%)	162/436 (37.16%)
Mucosal inflammation	65/446 (14.57%)	31/436 (7.11%)
Oedema peripheral	27/446 (6.05%)	26/436 (5.96%)
Pyrexia	64/446 (14.35%)	38/436 (8.72%)
Hepatobiliary disorders		

	Cetuximab Plus Capecitabine Plus Cisplatin	Capecitabine Plus Cisplatin
	Affected/At Risk (%)	Affected/At Risk (%)
Hyperbilirubinaemia	25/446 (5.61%)	11/436 (2.52%)
Infections and infestations		
Paronychia	63/446 (14.13%)	3/436 (0.69%)
Investigations		
Alanine aminotransferase increased	24/446 (5.38%)	16/436 (3.67%)
Aspartate aminotransferase increased	26/446 (5.83%)	13/436 (2.98%)
Blood creatinine increased	29/446 (6.5%)	37/436 (8.49%)
Glomerular filtration rate decreased	30/446 (6.73%)	35/436 (8.03%)
Haemoglobin decreased	37/446 (8.3%)	37/436 (8.49%)
Neutrophil count decreased	20/446 (4.48%)	22/436 (5.05%)
Platelet count decreased	17/446 (3.81%)	22/436 (5.05%)
Weight decreased	107/446 (23.99%)	77/436 (17.66%)
Metabolism and nutrition disorders		
Decreased appetite	221/446 (49.55%)	201/436 (46.1%)
Dehydration	29/446 (6.5%)	14/436 (3.21%)
Hypoalbuminaemia	39/446 (8.74%)	24/436 (5.5%)
Hypocalcaemia	67/446 (15.02%)	38/436 (8.72%)
Hypokalaemia	86/446 (19.28%)	56/436 (12.84%)
Hypomagnesaemia	133/446 (29.82%)	60/436 (13.76%)
Hyponatraemia	42/446 (9.42%)	34/436 (7.8%)
Hypophosphataemia	29/446 (6.5%)	13/436 (2.98%)
Musculoskeletal and connective tissue disorders		
Back pain	35/446 (7.85%)	19/436 (4.36%)
Nervous system disorders		
Dizziness	66/446 (14.8%)	45/436 (10.32%)
Dysgeusia	32/446 (7.17%)	29/436 (6.65%)

	Cetuximab Plus Capecitabine Plus Cisplatin	Capecitabine Plus Cisplatin
	Affected/At Risk (%)	Affected/At Risk (%)
Headache	31/446 (6.95%)	22/436 (5.05%)
Neuropathy peripheral	23/446 (5.16%)	41/436 (9.4%)
Paraesthesia	20/446 (4.48%)	27/436 (6.19%)
Peripheral sensory neuropathy	33/446 (7.4%)	27/436 (6.19%)
Psychiatric disorders		
Insomnia	41/446 (9.19%)	32/436 (7.34%)
Respiratory, thoracic and mediastinal disorders		
Cough	38/446 (8.52%)	19/436 (4.36%)
Dyspnoea	37/446 (8.3%)	21/436 (4.82%)
Hiccups	29/446 (6.5%)	47/436 (10.78%)
Skin and subcutaneous tissue disorders		
Acne	54/446 (12.11%)	1/436 (0.23%)
Alopecia	28/446 (6.28%)	19/436 (4.36%)
Dermatitis acneiform	78/446 (17.49%)	0/436 (0%)
Dry skin	56/446 (12.56%)	11/436 (2.52%)
Palmar-plantar erythrodysaesthesia syndrome	162/446 (36.32%)	97/436 (22.25%)
Rash	194/446 (43.5%)	23/436 (5.28%)
Skin fissures	28/446 (6.28%)	1/436 (0.23%)
Skin hyperpigmentation	15/446 (3.36%)	27/436 (6.19%)

Limitations and Caveats

[Not specified]

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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