ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: 03/28/2014

ClinicalTrials.gov ID: NCT00705016

Study Identification

Unique Protocol ID:	EMR 200052-013
Brief Title:	Cilengitide in Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN) (ADVANTAGE)
Official Title:	Open-label, Randomized, Controlled Phase I/II Study of Cilengitide to Evaluate the Safety and Efficacy of the Combination of Different Regimens of Cilengitide Added to Cisplatin, 5-FU, and Cetuximab in Subjects With Recurrent/Metastatic Squamous Cell Cancer of the Head and Neck
Secondary IDs:	2008-000615-15 [EudraCT Number]

Study Status

Record Verification:	March 2014
Overall Status:	Completed
Study Start:	October 2008
Primary Completion:	September 2011 [Actual]
Study Completion:	June 2013 [Actual]

Sponsor/Collaborators

Sponsor:	Merck KGaA
Responsible Party:	Sponsor
Collaborators:	

Oversight

FDA Regulated?:	No

IND/IDE Protocol?:	No
Review Board:	Approval Status: Approved Approval Number: 8/23/119 Board Name: Ethisch Comité UZ Antwerpen Board Affiliation: University Hospital Antwerpen Phone: Email: ethisch.comite@uza.be
Data Monitoring?:	Yes
Plan to Share Data?:	
Oversight Authorities:	Germany: Federal Institute for Drugs and Medical Devices Belgium: Federal Agency for Medicinal Products and Health Products France: Afssaps - Agence française de sécurité sanitaire des produits de santé (Saint-Denis) Austria: Agency for Health and Food Safety Switzerland: Swissmedic Spain: Spanish Agency of Medicines Hungary: National Institute of Pharmacy Italy: The Italian Medicines Agency Poland: Office for Registration of Medicinal Products, Medical Devices and Biocidal Products

Study Description

Brief Summary:

The purpose of this open-label, randomized, controlled, Phase 1/2 study of the integrin inhibitor cilengitide is to evaluate the safety and efficacy of the combination of different regimens of cilengitide added to cisplatin, 5-fluorouracil (5-FU), and cetuximab in participants with recurrent/metastatic squamous cell carcinoma of the head and neck (SCCHN).

The Phase 1 part was conducted in dedicated study centers. In the Phase 2 part of this trial, cilengitide is administered at two different doses to two experimental groups. The third group will only receive cisplatin, 5-FU and cetuximab. In the Phase 1 part of this trial, the dose of cilengitide in combination with cisplatin, 5-FU and cetuximab was determined.

Cilengitide is an experimental anti-cancer substance interacting with so-called integrins. Integrins are protein molecules that are known to be present on the surface of certain cancer cells. Integrins are also found on certain cells that belong to growing blood vessels (endothelial cells). Integrins potentially facilitate the blood vessels' support of the tumor (angiogenesis) as well as the tumor's growth and further spread throughout the body (metastasis). By inhibiting integrins on the tumor cell surface, cilengitide potentially kills cancer cells, and potentially sensitizes cancer cells to other co-administered therapeutics. By inhibiting integrins on the endothelial cell surface, it potentially inhibits the ingrowth of additional blood vessels towards the tumor.

Cilengitide is given as an intravenous infusion (given by a drip in one vein of your arm). If any unacceptable side effect occurs, treatment with the study drug will be stopped.

Detailed Description:

Conditions

Conditions:	Squamous Cell Cancer
Keywords:	Randomized treatment open-label controlled recurrent metastatic SCCHN suitable for local therapy

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 1/Phase 2
Intervention Model:	Parallel Assignment
Number of Arms:	3
Masking:	Open Label
Allocation:	Randomized
Endpoint Classification:	Safety/Efficacy Study
Enrollment:	184 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Cilengitide 2000 mg once weekly+Cetuximab+5-FU+Cisplatin	Drug: Cilengitide 2000 mg once weekly Cilengitide 500 milligram (mg) will be administered as an intravenous infusion over 60 minutes, daily from Day 1 to 4 of the first week of each 3-week cycle, subsequently followed by 2000 mg dose of cilengitide on Day 8 and 15 of every cycle for a total of 6 cycles (18 weeks) or until PD, unacceptable toxicity or withdrawal for any other reason. After 6 cycles, participants received cilengitide 2000 mg once weekly until PD, unacceptable toxicity or withdrawal for any other reason. Drug: Cetuximab Cetuximab will be administered as 250 milligram per square meter (mg/m^2) as infusion (initial starting dose of 400 mg/m^2) on Day 1, 8 and 15

Arms	Assigned Interventions
	of each 3-week treatment cycle. Cetuximab will be administered for a total of 6 cycles (18 weeks) or until PD, unacceptable toxicity or withdrawal for any other reason. After 6 cycles, participants received Cetuximab 250 mg/m^2 once weekly until PD, unacceptable toxicity or withdrawal for any other reason. Other Names: • Erbitux® Drug: 5-fluorouracil (5-FU) 5-FU will be administered as an intravenous continuous infusion at a dose of 1000 mg/m^2 daily from Day 1 to 4 of each 3-week treatment cycle. 5-FU will be administered for a total of 6 cycles (18 weeks), or until PD, unacceptable toxicity, or withdrawal for any other reason, whichever occur first. Drug: Cisplatin Cisplatin will be administered as an intravenous infusion over 60 minutes, at a dose 100 mg/m^2 on Day 1 of each 3-week treatment cycle. Cisplatin will be administered for a total of 6 cycles (18 weeks), or until PD, unacceptable toxicity, or withdrawal for any other reason, whichever occur first.
Experimental: Cilengitide 2000 mg twice weekly+Cetuximab+5-FU+Cisplatin	Drug: Cilengitide 2000 mg twice weekly Cilengitide 2000 mg will be administered as an intravenous infusion over 60 minutes, twice weekly on Day 1, 4, 8, 11, 15, and 18 of each 3-week cycle for a total of 6 cycles (18 weeks) or until PD, unacceptable toxicity or withdrawal for any other reason. After 6 cycles, participants will receive cilengitide 2000 mg once weekly until PD, unacceptable toxicity or withdrawal for any other reason. Drug: Cetuximab Cetuximab will be administered as 250 milligram per square meter (mg/m^2) as infusion (initial starting dose of 400 mg/m^2) on Day 1, 8 and 15 of each 3-week treatment cycle. Cetuximab will be administered for a total of 6 cycles (18 weeks) or until PD, unacceptable toxicity or withdrawal for any other reason. After 6 cycles, participants received Cetuximab 250 mg/m^2 once weekly until PD, unacceptable toxicity or withdrawal for any other reason. Other Names: • Erbitux® Drug: 5-fluorouracil (5-FU) 5-FU will be administered as an intravenous continuous infusion at a dose of 1000 mg/m^2 daily from Day 1 to 4 of each 3-week treatment cycle. 5-FU will be administered for a total of 6 cycles (18 weeks), or until PD, unacceptable toxicity, or withdrawal for any other reason, whichever occur first.

Arms	Assigned Interventions
	Drug: Cisplatin Cisplatin will be administered as an intravenous infusion over 60 minutes, at a dose 100 mg/m^2 on Day 1 of each 3-week treatment cycle. Cisplatin will be administered for a total of 6 cycles (18 weeks), or until PD, unacceptable toxicity, or withdrawal for any other reason, whichever occur first.
Active Comparator: Cetuximab+5-FU+Cisplatin	Drug: Cetuximab Cetuximab will be administered as 250 milligram per square meter (mg/m^2) as infusion (initial starting dose of 400 mg/m^2) on Day 1, 8 and 15 of each 3-week treatment cycle. Cetuximab will be administered for a total of 6 cycles (18 weeks) or until PD, unacceptable toxicity or withdrawal for any other reason. After 6 cycles, participants received Cetuximab 250 mg/m^2 once weekly until PD, unacceptable toxicity or withdrawal for any other reason. Other Names: • Erbitux® Drug: 5-fluorouracil (5-FU) 5-FU will be administered as an intravenous continuous infusion at a dose of 1000 mg/m^2 daily from Day 1 to 4 of each 3-week treatment cycle. 5-FU will be administered for a total of 6 cycles (18 weeks), or until PD, unacceptable toxicity, or withdrawal for any other reason, whichever occur first. Drug: Cisplatin Cisplatin will be administered as an intravenous infusion over 60 minutes, at a dose 100 mg/m^2 on Day 1 of each 3-week treatment cycle. Cisplatin will be administered for a total of 6 cycles (18 weeks), or until PD, unacceptable toxicity, or withdrawal for any other reason, whichever occur first.

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age:	18 Years
Maximum Age:	
Gender:	Both
Accepts Healthy Volunteers?:	No

Criteria: Inclusion Criteria:

- Histologically or cytologically confirmed diagnosis of SCCHN
- At least one measurable lesion either by computerized tomography (CT) scan or magnetic resonance imaging (MRI)
- Karnofsky performance status (KPS) of greater than or equal to 70 or eastern cooperative oncology group performance status (ECOG PS) of 0-1 at trial entry

Exclusion Criteria:

- Prior systemic chemotherapy, except if given as part of a multimodal treatment for locally advanced disease, which was completed more than 6 months prior to trial entry
- Surgery (excluding prior diagnostic biopsy) or irradiation within 4 weeks before trial entry
- Nasopharyngeal Carcinoma
- Documented or symptomatic brain or leptomeningeal metastasis
- Previous treatment with epidermal growth factor receptor (EGFR) targeting therapy or signal transduction inhibitors

Contacts/Locations

Study Officials: Jan Vermorken, MD, PhD
Study Principal Investigator
University Hospital Antwerp

Locations: Belgium
Research Site
Edegem (Antwerp), Belgium

Germany
Research Site
Hamburg, Germany

Research Site
Berlin, Germany

France
Research Site
Villejuif, France

Spain
Research Site
L'Hospitalet de Llobregat, Spain

Austria
Research Site
Salzburg, Austria

Belgium
Research Site
Namur, Belgium

Germany
Research Site
Essen, Germany

Research Site
Aachen, Germany

Research Site
Stuttgart, Germany

Research Site
Heidelberg, Germany

Hungary
Research Site
Nyiregyhaza, Hungary

Italy
Research Site
Milano, Italy

Belgium
Research Site
Leuven, Belgium

Research Site
Bruxelles, Belgium

France
Research Site
Tours, France

Research Site
Montpellier, France

Research Site
Nice, France

Hungary
Research Site
Budapest, Hungary

Austria
Research Site
Wien, Austria

Belgium
Research Site
Antwerp, Belgium

France
Research Site
Vandoeuvre les Nancy, France

Research Site
Toulouse, France

Research Site
Lille cedex, France

Germany
Research Site
Jena, Germany

Hungary
Research Site
Gyor, Hungary

Italy
Research Site
La Spezia, Italy

Research Site
Napoli, Italy

Switzerland
Research Site
Geneva, Switzerland

Spain
Research Site
Velencia, Spain

Poland
Research Site
Warsaw, Poland

Research Site

Gliwice, Poland

Belgium
Research Site
Gent, Belgium

Germany
Research Site
Leipzig, Germany

Research Site
Rostock, Germany

Spain
Research Site
Madrid, Spain

Switzerland
Research Site
Basel, Switzerland

References

Citations: [Study Results] Vermorken JB, Peyrade F, Krauss J, Mesía R, Remenar E, Gauler TC, Keilholz U, Delord JP, Schafhausen P, Erfán J, Brümmendorf TH, Iglesias L, Bethe U, Hicking C, Clement PM. Cisplatin, 5-fluorouracil, and cetuximab (PFE) with or without cilengitide in recurrent/metastatic squamous cell carcinoma of the head and neck: results of the randomized phase I/II ADVANTAGE trial (phase II part). Ann Oncol. 2014 Mar;25(3):682-8. doi: 10.1093/annonc/mdu003. PubMed 24567516

Links:

Study Data/Documents:

Participant Flow

Reporting Groups

	Description
Cilengitide 2000 mg Once Weekly +Cetuximab+5-FU+Cisplatin	Cilengitide 500 milligram (mg) intravenous infusion over 60 minutes, daily from Day 1 to 4 of the first week of each 3-week cycle, subsequently followed by cilengitide 2000 mg once weekly along with cetuximab 250 milligram per square meter (mg/m^2) intravenous infusion (initial starting dose of 400 mg/m^2) once weekly, 5-fluorouracil (5-FU) 1000 mg/m^2 intravenous continuous infusion daily from Day 1 to 4 and cisplatin 100 mg/m^2 intravenous infusion over 60 minutes on Day 1, of each 3-week treatment cycle for a total of 6 cycles (18 weeks) or until progressive disease (PD), unacceptable toxicity or withdrawal for any other reason. After 6 cycles, participants received cilengitide 2000 mg once weekly along with cetuximab 250 mg/m^2 intravenous infusion until PD, unacceptable toxicity or withdrawal for any other reason.
Cilengitide 2000 mg Twice Weekly +Cetuximab+5-FU+Cisplatin	Cilengitide 2000 mg intravenous infusion over 60 minutes twice weekly along with cetuximab 250 mg/m^2 intravenous infusion (initial starting dose of 400 mg/m^2) once weekly, 5-fluorouracil (5-FU) 1000 mg/m^2 intravenous continuous infusion daily from Day 1 to 4 and cisplatin 100 mg/m^2 intravenous infusion over 60 minutes on Day 1, of each 3-week treatment cycle for a total of 6 cycles (18 weeks) or until PD, unacceptable toxicity or withdrawal for any other reason. After 6 cycles, participants received cilengitide 2000 mg once weekly along with cetuximab 250 mg/m^2 intravenous infusion until PD, unacceptable toxicity or withdrawal for any other reason.
Cetuximab+5-FU+Cisplatin	Cetuximab 250 mg/m^2 intravenous infusion (initial starting dose of 400 mg/m^2) once weekly along with 5-fluorouracil (5-FU) 1000 mg/m^2 intravenous continuous infusion daily from Day 1 to 4 and cisplatin 100 mg/m^2 intravenous infusion over 60 minutes on Day 1, of each 3-week treatment cycle for a total of 6 cycles (18 weeks) or until PD, unacceptable toxicity or withdrawal for any other reason. After 6 cycles, participants received cetuximab 250 mg/m^2 intravenous infusion until PD, unacceptable toxicity or withdrawal for any other reason.

Overall Study

	Cilengitide 2000 mg Once Weekly+Cetuximab +5-FU+Cisplatin	Cilengitide 2000 mg Twice Weekly+Cetuximab +5-FU+Cisplatin	Cetuximab+5-FU+Cisplatin
Started	62	60	62
Completed	2	2	4
Not Completed	60	58	58
Adverse Event	6	11	10
Death	5	7	5

	Cilengitide 2000 mg Once Weekly+Cetuximab +5-FU+Cisplatin	Cilengitide 2000 mg Twice Weekly+Cetuximab +5-FU+Cisplatin	Cetuximab+5-FU+Cisplatin
Protocol Violation	0	1	1
Withdrawal by Subject	4	3	2
Progressive Disease	33	29	33
Symptomatic Deterioration	3	1	1
Unspecified	9	6	6

Baseline Characteristics

Analysis Population Description

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

Reporting Groups

	Description
Cilengitide 2000 mg Once Weekly +Cetuximab+5-FU+Cisplatin	Cilengitide 500 milligram (mg) intravenous infusion over 60 minutes, daily from Day 1 to 4 of the first week of each 3-week cycle, subsequently followed by cilengitide 2000 mg once weekly along with cetuximab 250 milligram per square meter (mg/m^2) intravenous infusion (initial starting dose of 400 mg/m^2) once weekly, 5-fluorouracil (5-FU) 1000 mg/m^2 intravenous continuous infusion daily from Day 1 to 4 and cisplatin 100 mg/m^2 intravenous infusion over 60 minutes on Day 1, of each 3-week treatment cycle for a total of 6 cycles (18 weeks) or until progressive disease (PD), unacceptable toxicity or withdrawal for any other reason. After 6 cycles, participants received cilengitide 2000 mg once weekly along with cetuximab 250 mg/m^2 intravenous infusion until PD, unacceptable toxicity or withdrawal for any other reason.
Cilengitide 2000 mg Twice Weekly +Cetuximab+5-FU+Cisplatin	Cilengitide 2000 mg intravenous infusion over 60 minutes twice weekly along with cetuximab 250 mg/m^2 intravenous infusion (initial starting dose of 400 mg/m^2) once weekly, 5-fluorouracil (5-FU) 1000 mg/m^2 intravenous continuous infusion daily from Day 1 to 4 and cisplatin 100 mg/m^2 intravenous infusion over 60 minutes on Day 1, of each 3-week treatment cycle for a total of 6 cycles (18 weeks) or until PD, unacceptable toxicity or withdrawal for any other reason. After 6 cycles, participants received cilengitide 2000 mg once weekly along with cetuximab 250 mg/m^2 intravenous infusion until PD, unacceptable toxicity or withdrawal for any other reason.
Cetuximab+5-FU+Cisplatin	Cetuximab 250 mg/m^2 intravenous infusion (initial starting dose of 400 mg/m^2) once weekly along with 5-fluorouracil (5-FU) 1000 mg/m^2 intravenous continuous infusion daily from Day 1 to 4 and cisplatin 100 mg/m^2 intravenous infusion over 60 minutes on Day 1, of each 3-week treatment cycle for a total of 6 cycles (18 weeks) or until PD, unacceptable toxicity or withdrawal for any other reason. After 6 cycles, participants received cetuximab 250 mg/m^2 intravenous infusion until PD, unacceptable toxicity or withdrawal for any other reason.

Baseline Measures

	Cilengitide 2000 mg Once Weekly+Cetuximab +5-FU+Cisplatin	Cilengitide 2000 mg Twice Weekly+Cetuximab +5-FU+Cisplatin	Cetuximab+5-FU+Cisplatin	Total
Number of Participants	62	60	62	184
Age, Continuous [1] [units: years] Mean (Standard Deviation)	59.1 (7.4)	56.8 (7.9)	58.6 (8.1)	58.2 (7.8)
Age, Customized [1] [units: participants]				
Less than (<) 65 years	47	48	46	141
Greater than or equal to (>=) 65 years	15	12	15	42
Gender, Male/Female [units: participants]				
Female	8	11	6	25
Male	54	49	56	159
Karnofsky Performance Status [2] [units: participants]				
< 80 (Karnofsky Score)	7	6	5	18
>= 80 (Karnofsky Score)	55	54	57	166
Extent of disease at study entry [units: participants]				
Recurrence	30	32	31	93
Distant Metastasis	32	28	31	91
Tumor Grade [3] [units: participants]				
Well or moderately differentiated	46	39	35	120
Poorly differentiated	11	19	22	52

	Cilengitide 2000 mg Once Weekly+Cetuximab +5-FU+Cisplatin	Cilengitide 2000 mg Twice Weekly+Cetuximab +5-FU+Cisplatin	Cetuximab+5-FU+Cisplatin	Total
Site of origin of tumor [units: participants]				
Oropharynx	25	23	21	69
Hypopharynx	10	14	14	38
Larynx	14	15	13	42
Oral cavity	11	6	11	28
Other, including non-classifiable	2	2	3	7

[1] Out of a total of 62 participants in Cetuximab + 5-FU + Cisplatin group, data for baseline measure (age) was available for 61 participants only.

[2] Karnofsky performance status score ranged from 100 to 0; 100: Normal; 90: Able to Carry on normal Activity; 80: Normal Activity with Effort; Some Signs or Symptoms of Disease; 70: Cares for Self, Unable to Carry on Normal Activity or to Do Active Work; 60: Requires Occasional Assistance but is Able to Care for Most of Needs; 50: Requires Considerable Assistance and Frequent Medical Care; 40: Disabled, Requires Special Care and Assistance; 30: Severely Disabled; Hospitalization Indicated Although Death is Not Imminent; 20: Very Sick; 10: Moribund, Fatal Processes Progressing Rapidly; 0: Death.

[3] Out of a total of 62 participants in Cilengitide 2000 mg once weekly + Cetuximab + 5-FU + Cisplatin group, 60 participants in Cilengitide 2000 mg twice weekly + Cetuximab + 5-FU + Cisplatin group, and 62 participants in Cetuximab + 5-FU + Cisplatin group, data for baseline measure (Tumor grade) was available for 57, 58 and 57 participants only, respectively. Tumor grades were divided in to well or moderately differentiated and poorly differentiated.

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Progression-free Survival (PFS) Time: Investigator Read
Measure Description	The PFS is defined as the duration from randomization until radiological progression (based on response evaluation criteria in solid tumors [RECIST] Version 1.0) or death due to any cause. Only deaths within 84 days of last tumor assessment are considered. Participants without event are censored on the date of last tumor assessment. Investigator read is the assessment of all imaging by the treating physician at the local trial site.
Time Frame	Time from randomization to disease progression, death or last tumor assessment, reported between day of first participant randomized, 03 July 2009, until cut-off date (03 September 2011)
Safety Issue?	No

Analysis Population Description

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

Reporting Groups

	Description
Cilengitide 2000 mg Once Weekly +Cetuximab+5-FU+Cisplatin	Cilengitide 500 milligram (mg) intravenous infusion over 60 minutes, daily from Day 1 to 4 of the first week of each 3-week cycle, subsequently followed by cilengitide 2000 mg once weekly along with cetuximab 250 milligram per square meter (mg/m^2) intravenous infusion (initial starting dose of 400 mg/m^2) once weekly, 5-fluorouracil (5-FU) 1000 mg/m^2 intravenous continuous infusion daily from Day 1 to 4 and cisplatin 100 mg/m^2 intravenous infusion over 60 minutes on Day 1, of each 3-week treatment cycle for a total of 6 cycles (18 weeks) or until progressive disease (PD), unacceptable toxicity or withdrawal for any other reason. After 6 cycles, participants received cilengitide 2000 mg once weekly along with cetuximab 250 mg/m^2 intravenous infusion until PD, unacceptable toxicity or withdrawal for any other reason.
Cilengitide 2000 mg Twice Weekly +Cetuximab+5-FU+Cisplatin	Cilengitide 2000 mg intravenous infusion over 60 minutes twice weekly along with cetuximab 250 mg/m^2 intravenous infusion (initial starting dose of 400 mg/m^2) once weekly, 5-fluorouracil (5-FU) 1000 mg/m^2 intravenous continuous infusion daily from Day 1 to 4 and cisplatin 100 mg/m^2 intravenous infusion over 60 minutes on Day 1, of each 3-week treatment cycle for a total of 6 cycles (18 weeks) or until PD, unacceptable toxicity or withdrawal for any other reason. After 6 cycles, participants received cilengitide 2000 mg once weekly along with cetuximab 250 mg/m^2 intravenous infusion until PD, unacceptable toxicity or withdrawal for any other reason.
Cetuximab+5-FU+Cisplatin	Cetuximab 250 mg/m^2 intravenous infusion (initial starting dose of 400 mg/m^2) once weekly along with 5-fluorouracil (5-FU) 1000 mg/m^2 intravenous continuous infusion daily from Day 1 to 4 and cisplatin 100 mg/m^2 intravenous infusion over 60 minutes on Day 1, of each 3-week treatment cycle for a total of 6 cycles (18 weeks) or until PD, unacceptable toxicity or withdrawal for any other reason. After 6 cycles, participants received cetuximab 250 mg/m^2 intravenous infusion until PD, unacceptable toxicity or withdrawal for any other reason.

Measured Values

	Cilengitide 2000 mg Once Weekly+Cetuximab +5-FU+Cisplatin	Cilengitide 2000 mg Twice Weekly+Cetuximab +5-FU+Cisplatin	Cetuximab+5-FU+Cisplatin
Number of Participants Analyzed	62	60	62
Progression-free Survival (PFS) Time: Investigator Read [units: months] Median (95% Confidence Interval)	6.4 (5.4 to 8.7)	5.6 (4.0 to 6.1)	5.7 (4.2 to 9.5)

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

Statistical Analysis Overview	Comparison Groups	Cilengitide 2000 mg Once Weekly+Cetuximab+5-FU+Cisplatin, Cetuximab+5-FU+Cisplatin
	Comments	Sample size of 177 subjects was estimated such that the treatment group with the best PFS result had a 90% probability of emerging as the one with the smaller observed log Hazard ratio (HR), if there was an underlying difference of 2.2 months between the arms in the median PFS (7.8 months in the best group and 5.6 months in the other 2 groups). It was assumed that the accrual and follow-up time would take 1 year each, and that the drop-out rate was 8%.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.885
	Comments	The Type I error was not taken into account, since the sample size calculation is based on selection theory.
	Method	Other [Cox proportional hazards model]
	Comments	Stratification factor: Karnofsky performance status (KPS) <80/>=80

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	1.03
	Confidence Interval	(2-Sided) 95% 0.67 to 1.59
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Progression-free Survival (PFS) Time: Investigator Read

Statistical Analysis Overview	Comparison Groups	Cilengitide 2000 mg Twice Weekly+Cetuximab+5-FU+Cisplatin, Cetuximab+5-FU+Cisplatin
	Comments	Sample size of 177 subjects was estimated such that the treatment group with the best PFS result had a 90% probability of emerging as the one with the smaller observed log HR, if there was an underlying difference of 2.2 months between the arms in the median PFS (7.8 months in the best group and 5.6 months in the other 2 groups). It was assumed that the accrual and follow-up time would take 1 year each, and that the drop-out rate was 8%.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.054
	Comments	The Type I error was not taken into account, since the sample size calculation is based on selection theory.
	Method	Other [Cox proportional hazards model]
	Comments	Stratification factor: Karnofsky performance status (KPS) <80/>=80

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	1.55
	Confidence Interval	(2-Sided) 95% 0.99 to 2.43
	Estimation Comments	[Not specified]

2. Secondary Outcome Measure:

Measure Title	Overall Survival (OS) Time
Measure Description	The OS time is defined as the time from randomization 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 to death, reported between day of first participant randomized, 03 July 2009, until cut-off date (03 September 2011)
Safety Issue?	No

Analysis Population Description

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

Reporting Groups

	Description
Cilengitide 2000 mg Once Weekly +Cetuximab+5-FU+Cisplatin	Cilengitide 500 milligram (mg) intravenous infusion over 60 minutes, daily from Day 1 to 4 of the first week of each 3-week cycle, subsequently followed by cilengitide 2000 mg once weekly along with cetuximab 250 milligram per square meter (mg/m^2) intravenous infusion (initial starting dose of 400 mg/m^2) once weekly, 5-fluorouracil (5-FU) 1000 mg/m^2 intravenous continuous infusion daily from Day 1 to 4 and cisplatin 100 mg/m^2 intravenous infusion over 60 minutes on Day 1, of each 3-week treatment cycle for a total of 6 cycles (18 weeks) or until progressive disease (PD), unacceptable toxicity or withdrawal for any other reason. After 6 cycles, participants received cilengitide 2000 mg once weekly along with cetuximab 250 mg/m^2 intravenous infusion until PD, unacceptable toxicity or withdrawal for any other reason.

	Description
Cilengitide 2000 mg Twice Weekly +Cetuximab+5-FU+Cisplatin	Cilengitide 2000 mg intravenous infusion over 60 minutes twice weekly along with cetuximab 250 mg/m^2 intravenous infusion (initial starting dose of 400 mg/m^2) once weekly, 5-fluorouracil (5-FU) 1000 mg/m^2 intravenous continuous infusion daily from Day 1 to 4 and cisplatin 100 mg/m^2 intravenous infusion over 60 minutes on Day 1, of each 3-week treatment cycle for a total of 6 cycles (18 weeks) or until PD, unacceptable toxicity or withdrawal for any other reason. After 6 cycles, participants received cilengitide 2000 mg once weekly along with cetuximab 250 mg/m^2 intravenous infusion until PD, unacceptable toxicity or withdrawal for any other reason.
Cetuximab+5-FU+Cisplatin	Cetuximab 250 mg/m^2 intravenous infusion (initial starting dose of 400 mg/m^2) once weekly along with 5-fluorouracil (5-FU) 1000 mg/m^2 intravenous continuous infusion daily from Day 1 to 4 and cisplatin 100 mg/m^2 intravenous infusion over 60 minutes on Day 1, of each 3-week treatment cycle for a total of 6 cycles (18 weeks) or until PD, unacceptable toxicity or withdrawal for any other reason. After 6 cycles, participants received cetuximab 250 mg/m^2 intravenous infusion until PD, unacceptable toxicity or withdrawal for any other reason.

Measured Values

	Cilengitide 2000 mg Once Weekly+Cetuximab +5-FU+Cisplatin	Cilengitide 2000 mg Twice Weekly+Cetuximab +5-FU+Cisplatin	Cetuximab+5-FU+Cisplatin
Number of Participants Analyzed	62	60	62
Overall Survival (OS) Time [units: months] Median (95% Confidence Interval)	12.4 (9.4 to 14.5)	10.6 (9.0 to 14.8)	11.6 (7.1 to 16.4)

Statistical Analysis 1 for Overall Survival (OS) Time

Statistical Analysis Overview	Comparison Groups	Cilengitide 2000 mg Once Weekly+Cetuximab+5-FU+Cisplatin, Cetuximab+5-FU+Cisplatin
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.800
	Comments	Secondary analyses of efficacy were performed to support the results of the primary analysis and considered as purely exploratory and no adjustment for multiplicity has been done.
	Method	Other [Cox proportional hazards model]

	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	0.94
	Confidence Interval	(2-Sided) 95% 0.61 to 1.47
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Overall Survival (OS) Time

Statistical Analysis Overview	Comparison Groups	Cilengitide 2000 mg Twice Weekly+Cetuximab+5-FU+Cisplatin, Cetuximab+5-FU+Cisplatin
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.878
	Comments	[Not specified]
	Method	Other [Cox proportional hazards model]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	1.04
	Confidence Interval	(2-Sided) 95% 0.66 to 1.63
	Estimation Comments	[Not specified]

3. Secondary Outcome Measure:

Measure Title	Best Overall Response (BOR) Rate
Measure Description	The BOR rate is defined as the percentage of the participants having achieved confirmed complete response (CR) or partial response (PR) as the best overall response according to radiological assessments (based on RECIST Version 1.0).
Time Frame	Evaluations will be performed every 6 weeks until progression reported between day of first participant randomized, 03 July 2009, until cut-off date (03 September 2011)
Safety Issue?	No

Analysis Population Description

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

Reporting Groups

	Description
Cilengitide 2000 mg Once Weekly +Cetuximab+5-FU+Cisplatin	Cilengitide 500 milligram (mg) intravenous infusion over 60 minutes, daily from Day 1 to 4 of the first week of each 3-week cycle, subsequently followed by cilengitide 2000 mg once weekly along with cetuximab 250 milligram per square meter (mg/m^2) intravenous infusion (initial starting dose of 400 mg/m^2) once weekly, 5-fluorouracil (5-FU) 1000 mg/m^2 intravenous continuous infusion daily from Day 1 to 4 and cisplatin 100 mg/m^2 intravenous infusion over 60 minutes on Day 1, of each 3-week treatment cycle for a total of 6 cycles (18 weeks) or until progressive disease (PD), unacceptable toxicity or withdrawal for any other reason. After 6 cycles, participants received cilengitide 2000 mg once weekly along with cetuximab 250 mg/m^2 intravenous infusion until PD, unacceptable toxicity or withdrawal for any other reason.
Cilengitide 2000 mg Twice Weekly +Cetuximab+5-FU+Cisplatin	Cilengitide 2000 mg intravenous infusion over 60 minutes twice weekly along with cetuximab 250 mg/m^2 intravenous infusion (initial starting dose of 400 mg/m^2) once weekly, 5-fluorouracil (5-FU) 1000 mg/m^2 intravenous continuous infusion daily from Day 1 to 4 and cisplatin 100 mg/m^2 intravenous infusion over 60 minutes on Day 1, of each 3-week treatment cycle for a total of 6 cycles (18 weeks) or until PD, unacceptable toxicity or withdrawal for any other reason. After 6 cycles, participants received cilengitide 2000 mg once weekly along with cetuximab 250 mg/m^2 intravenous infusion until PD, unacceptable toxicity or withdrawal for any other reason.
Cetuximab+5-FU+Cisplatin	Cetuximab 250 mg/m^2 intravenous infusion (initial starting dose of 400 mg/m^2) once weekly along with 5-fluorouracil (5-FU) 1000 mg/m^2 intravenous continuous infusion daily from Day 1 to 4 and cisplatin 100 mg/m^2 intravenous infusion over 60 minutes on Day 1, of each 3-week treatment cycle for a total of 6 cycles (18 weeks) or until PD, unacceptable toxicity or withdrawal for any other reason. After 6 cycles, participants received cetuximab 250 mg/m^2 intravenous infusion until PD, unacceptable toxicity or withdrawal for any other reason.

Measured Values

	Cilengitide 2000 mg Once Weekly+Cetuximab +5-FU+Cisplatin	Cilengitide 2000 mg Twice Weekly+Cetuximab +5-FU+Cisplatin	Cetuximab+5-FU+Cisplatin
Number of Participants Analyzed	62	60	62
Best Overall Response (BOR) Rate [units: percentage of participants] Number (95% Confidence Interval)	46.8 (34.0 to 59.9)	26.7 (16.1 to 39.7)	35.5 (23.7 to 48.7)

Statistical Analysis 1 for Best Overall Response (BOR) Rate

Statistical Analysis Overview	Comparison Groups	Cilengitide 2000 mg Once Weekly+Cetuximab+5-FU+Cisplatin, Cetuximab+5-FU+Cisplatin
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.205
	Comments	Secondary analyses of efficacy were performed to support the results of the primary analysis and considered as purely exploratory and no adjustment for multiplicity has been done.
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	1.595
	Confidence Interval	(2-Sided) 95% 0.776 to 3.276
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Best Overall Response (BOR) Rate

Statistical Analysis Overview	Comparison Groups	Cilengitide 2000 mg Twice Weekly+Cetuximab+5-FU+Cisplatin, Cetuximab+5-FU+Cisplatin
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.317
	Comments	Secondary analyses of efficacy were performed to support the results of the primary analysis and considered as purely exploratory and no adjustment for multiplicity has been done.
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	0.671
	Confidence Interval	(2-Sided) 95% 0.307 to 1.465
	Estimation Comments	[Not specified]

4. Secondary Outcome Measure:

Measure Title	Disease Control Rate
Measure Description	The disease control rate is defined as the percentage of participants having achieved confirmed CR, PR or stable disease (SD) as best overall response according to radiological assessments (based on RECIST Version 1.0).
Time Frame	Evaluations will be performed every 6 weeks until progression reported between day of first participant randomized, 03 July 2009, until cut-off date (03 September 2011)
Safety Issue?	No

Analysis Population Description

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

Reporting Groups

	Description
Cilengitide 2000 mg Once Weekly +Cetuximab+5-FU+Cisplatin	Cilengitide 500 milligram (mg) intravenous infusion over 60 minutes, daily from Day 1 to 4 of the first week of each 3-week cycle, subsequently followed by cilengitide 2000 mg once weekly along with cetuximab 250 milligram per square meter (mg/m^2) intravenous infusion (initial starting dose of 400 mg/m^2) once weekly, 5-fluorouracil (5-FU) 1000 mg/m^2 intravenous continuous infusion daily from Day 1 to 4 and cisplatin 100 mg/m^2 intravenous infusion over 60 minutes on Day 1, of each 3-week treatment cycle for a total of 6 cycles (18 weeks) or until progressive disease (PD), unacceptable toxicity or withdrawal for any other reason. After 6 cycles, participants received cilengitide 2000 mg once weekly along with cetuximab 250 mg/m^2 intravenous infusion until PD, unacceptable toxicity or withdrawal for any other reason.
Cilengitide 2000 mg Twice Weekly +Cetuximab+5-FU+Cisplatin	Cilengitide 2000 mg intravenous infusion over 60 minutes twice weekly along with cetuximab 250 mg/m^2 intravenous infusion (initial starting dose of 400 mg/m^2) once weekly, 5-fluorouracil (5-FU) 1000 mg/m^2 intravenous continuous infusion daily from Day 1 to 4 and cisplatin 100 mg/m^2 intravenous infusion over 60 minutes on Day 1, of each 3-week treatment cycle for a total of 6 cycles (18 weeks) or until PD, unacceptable toxicity or withdrawal for any other reason. After 6 cycles, participants received cilengitide 2000 mg once weekly along with cetuximab 250 mg/m^2 intravenous infusion until PD, unacceptable toxicity or withdrawal for any other reason.

	Description
Cetuximab+5-FU+Cisplatin	Cetuximab 250 mg/m^2 intravenous infusion (initial starting dose of 400 mg/m^2) once weekly along with 5-fluorouracil (5-FU) 1000 mg/m^2 intravenous continuous infusion daily from Day 1 to 4 and cisplatin 100 mg/m^2 intravenous infusion over 60 minutes on Day 1, of each 3-week treatment cycle for a total of 6 cycles (18 weeks) or until PD, unacceptable toxicity or withdrawal for any other reason. After 6 cycles, participants received cetuximab 250 mg/m^2 intravenous infusion until PD, unacceptable toxicity or withdrawal for any other reason.

Measured Values

	Cilengitide 2000 mg Once Weekly+Cetuximab +5-FU+Cisplatin	Cilengitide 2000 mg Twice Weekly+Cetuximab +5-FU+Cisplatin	Cetuximab+5-FU+Cisplatin
Number of Participants Analyzed	62	60	62
Disease Control Rate [units: percentage of participants] Number (95% Confidence Interval)	85.5 (74.2 to 93.1)	73.3 (60.3 to 83.9)	80.6 (68.6 to 89.6)

Statistical Analysis 1 for Disease Control Rate

Statistical Analysis Overview	Comparison Groups	Cilengitide 2000 mg Once Weekly+Cetuximab+5-FU+Cisplatin, Cetuximab+5-FU+Cisplatin
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.476
	Comments	Secondary analyses of efficacy were performed to support the results of the primary analysis and considered as purely exploratory and no adjustment for multiplicity has been done.
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	1.396
	Confidence Interval	(2-Sided) 95% 0.551 to 3.539

	Estimation Comments	[Not specified]

Statistical Analysis 2 for Disease Control Rate

Statistical Analysis Overview	Comparison Groups	Cilengitide 2000 mg Twice Weekly+Cetuximab+5-FU+Cisplatin, Cetuximab+5-FU+Cisplatin
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.347
	Comments	Secondary analyses of efficacy were performed to support the results of the primary analysis and considered as purely exploratory and no adjustment for multiplicity has been done.
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	0.668
	Confidence Interval	(2-Sided) 95% 0.287 to 1.555
	Estimation Comments	[Not specified]

5. Secondary Outcome Measure:

Measure Title	Time to Treatment Failure (TTF)
Measure Description	TTF is defined as the time from randomization to date of the first occurrence of; progression, discontinuation of treatment due to progression or adverse event, start of new anticancer therapy, withdrawal of consent, or death (within 84 days of last tumor assessment). 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, 03 July 2009, until cut-off date (03 September 2011)
Safety Issue?	No

Analysis Population Description

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

Reporting Groups

	Description
Cilengitide 2000 mg Once Weekly +Cetuximab+5-FU+Cisplatin	Cilengitide 500 milligram (mg) intravenous infusion over 60 minutes, daily from Day 1 to 4 of the first week of each 3-week cycle, subsequently followed by cilengitide 2000 mg once weekly along with cetuximab 250 milligram per square meter (mg/m^2) intravenous infusion (initial starting dose of 400 mg/m^2) once weekly, 5-fluorouracil (5-FU) 1000 mg/m^2 intravenous continuous infusion daily from Day 1 to 4 and cisplatin 100 mg/m^2 intravenous infusion over 60 minutes on Day 1, of each 3-week treatment cycle for a total of 6 cycles (18 weeks) or until progressive disease (PD), unacceptable toxicity or withdrawal for any other reason. After 6 cycles, participants received cilengitide 2000 mg once weekly along with cetuximab 250 mg/m^2 intravenous infusion until PD, unacceptable toxicity or withdrawal for any other reason.
Cilengitide 2000 mg Twice Weekly +Cetuximab+5-FU+Cisplatin	Cilengitide 2000 mg intravenous infusion over 60 minutes twice weekly along with cetuximab 250 mg/m^2 intravenous infusion (initial starting dose of 400 mg/m^2) once weekly, 5-fluorouracil (5-FU) 1000 mg/m^2 intravenous continuous infusion daily from Day 1 to 4 and cisplatin 100 mg/m^2 intravenous infusion over 60 minutes on Day 1, of each 3-week treatment cycle for a total of 6 cycles (18 weeks) or until PD, unacceptable toxicity or withdrawal for any other reason. After 6 cycles, participants received cilengitide 2000 mg once weekly along with cetuximab 250 mg/m^2 intravenous infusion until PD, unacceptable toxicity or withdrawal for any other reason.
Cetuximab+5-FU+Cisplatin	Cetuximab 250 mg/m^2 intravenous infusion (initial starting dose of 400 mg/m^2) once weekly along with 5-fluorouracil (5-FU) 1000 mg/m^2 intravenous continuous infusion daily from Day 1 to 4 and cisplatin 100 mg/m^2 intravenous infusion over 60 minutes on Day 1, of each 3-week treatment cycle for a total of 6 cycles (18 weeks) or until PD, unacceptable toxicity or withdrawal for any other reason. After 6 cycles, participants received cetuximab 250 mg/m^2 intravenous infusion until PD, unacceptable toxicity or withdrawal for any other reason.

Measured Values

	Cilengitide 2000 mg Once Weekly+Cetuximab +5-FU+Cisplatin	Cilengitide 2000 mg Twice Weekly+Cetuximab +5-FU+Cisplatin	Cetuximab+5-FU+Cisplatin
Number of Participants Analyzed	62	60	62
Time to Treatment Failure (TTF) [units: months] Median (95% Confidence Interval)	5.6 (4.2 to 6.9)	4.5 (2.9 to 5.6)	4.3 (3.8 to 7.3)

Statistical Analysis 1 for Time to Treatment Failure (TTF)

Statistical Analysis Overview	Comparison Groups	Cilengitide 2000 mg Once Weekly+Cetuximab+5-FU+Cisplatin, Cetuximab+5-FU+Cisplatin
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No

	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.294
	Comments	Secondary analyses of efficacy were performed to support the results of the primary analysis and considered as purely exploratory and no adjustment for multiplicity has been done.
	Method	Other [Cox proportional hazards model]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	1.23
	Confidence Interval	(2-Sided) 95% 0.84 to 1.81
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Time to Treatment Failure (TTF)

Statistical Analysis Overview	Comparison Groups	Cilengitide 2000 mg Twice Weekly+Cetuximab+5-FU+Cisplatin, Cetuximab+5-FU+Cisplatin
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.007
	Comments	Secondary analyses of efficacy were performed to support the results of the primary analysis and considered as purely exploratory and no adjustment for multiplicity has been done.
	Method	Other [Cox proportional hazards model]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	1.73
	Confidence Interval	(2-Sided) 95% 1.16 to 2.57
	Estimation Comments	[Not specified]

6. Secondary Outcome Measure:

Measure Title	Duration of Response
Measure Description	Duration of response is defined as the time from the first assessment of CR or PR until the date of the first occurrence of progressive disease (PD), or until the date of death.
Time Frame	Time from first assessment of CR or PR until PD, death or last tumor assessment, reported between day of first participant randomized, 03 July 2009, until cut-off date (03 September 2011)
Safety Issue?	No

Analysis Population Description

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

Reporting Groups

	Description
Cilengitide 2000 mg Once Weekly +Cetuximab+5-FU+Cisplatin	Cilengitide 500 milligram (mg) intravenous infusion over 60 minutes, daily from Day 1 to 4 of the first week of each 3-week cycle, subsequently followed by cilengitide 2000 mg once weekly along with cetuximab 250 milligram per square meter (mg/m^2) intravenous infusion (initial starting dose of 400 mg/m^2) once weekly, 5-fluorouracil (5-FU) 1000 mg/m^2 intravenous continuous infusion daily from Day 1 to 4 and cisplatin 100 mg/m^2 intravenous infusion over 60 minutes on Day 1, of each 3-week treatment cycle for a total of 6 cycles (18 weeks) or until progressive disease (PD), unacceptable toxicity or withdrawal for any other reason. After 6 cycles, participants received cilengitide 2000 mg once weekly along with cetuximab 250 mg/m^2 intravenous infusion until PD, unacceptable toxicity or withdrawal for any other reason.
Cilengitide 2000 mg Twice Weekly +Cetuximab+5-FU+Cisplatin	Cilengitide 2000 mg intravenous infusion over 60 minutes twice weekly along with cetuximab 250 mg/m^2 intravenous infusion (initial starting dose of 400 mg/m^2) once weekly, 5-fluorouracil (5-FU) 1000 mg/m^2 intravenous continuous infusion daily from Day 1 to 4 and cisplatin 100 mg/m^2 intravenous infusion over 60 minutes on Day 1, of each 3-week treatment cycle for a total of 6 cycles (18 weeks) or until PD, unacceptable toxicity or withdrawal for any other reason. After 6 cycles, participants received cilengitide 2000 mg once weekly along with cetuximab 250 mg/m^2 intravenous infusion until PD, unacceptable toxicity or withdrawal for any other reason.
Cetuximab+5-FU+Cisplatin	Cetuximab 250 mg/m^2 intravenous infusion (initial starting dose of 400 mg/m^2) once weekly along with 5-fluorouracil (5-FU) 1000 mg/m^2 intravenous continuous infusion daily from Day 1 to 4 and cisplatin 100 mg/m^2 intravenous infusion over 60 minutes on Day 1, of each 3-week treatment cycle for a total of 6 cycles (18 weeks) or until PD, unacceptable toxicity or withdrawal for any other reason. After 6 cycles, participants received cetuximab 250 mg/m^2 intravenous infusion until PD, unacceptable toxicity or withdrawal for any other reason.

Measured Values

	Cilengitide 2000 mg Once Weekly+Cetuximab +5-FU+Cisplatin	Cilengitide 2000 mg Twice Weekly+Cetuximab +5-FU+Cisplatin	Cetuximab+5-FU+Cisplatin
Number of Participants Analyzed	62	60	62
Duration of Response [units: months] Median (95% Confidence Interval)	5.8 (4.5 to 7.5)	4.1 (3.1 to 4.4)	6.4 (4.2 to 9.7)

Statistical Analysis 1 for Duration of Response

Statistical Analysis Overview	Comparison Groups	Cilengitide 2000 mg Once Weekly+Cetuximab+5-FU+Cisplatin, Cetuximab+5-FU+Cisplatin
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.391
	Comments	Secondary analyses of efficacy were performed to support the results of the primary analysis and considered as purely exploratory and no adjustment for multiplicity has been done.
	Method	Other [Cox proportional hazards model]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	1.30
	Confidence Interval	(2-Sided) 95% 0.71 to 2.39
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Duration of Response

Statistical Analysis Overview	Comparison Groups	Cilengitide 2000 mg Twice Weekly+Cetuximab+5-FU+Cisplatin, Cetuximab+5-FU+Cisplatin
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No

	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.007
	Comments	Secondary analyses of efficacy were performed to support the results of the primary analysis and considered as purely exploratory and no adjustment for multiplicity has been done.
	Method	Other [Cox proportional hazards model]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	2.60
	Confidence Interval	(2-Sided) 95% 1.30 to 5.21
	Estimation Comments	[Not specified]

7. Secondary Outcome Measure:

Measure Title	Safety - Number of Participants Experiencing Any Adverse Event
Measure Description	Please refer to Adverse Events section for details of individual serious adverse events and other adverse events
Time Frame	Time from first assessment of CR or PR until PD, death or last tumor assessment, reported between day of first participant randomized, 03 July 2009, until cut-off date (03 September 2011)
Safety Issue?	Yes

Analysis Population Description

Safety population included all participants who were administered any dose of the trial medication, that is, cilengitide, cisplatin, 5-FU, or cetuximab.

Reporting Groups

	Description
Cilengitide 2000 mg Once Weekly +Cetuximab+5-FU+Cisplatin	Cilengitide 500 milligram (mg) intravenous infusion over 60 minutes, daily from Day 1 to 4 of the first week of each 3-week cycle, subsequently followed by cilengitide 2000 mg once weekly along with cetuximab 250 milligram per square meter (mg/m^2) intravenous infusion (initial starting dose of 400 mg/m^2) once weekly, 5-fluorouracil (5-FU) 1000 mg/m^2 intravenous continuous infusion daily from Day 1 to 4 and cisplatin 100 mg/m^2 intravenous infusion over 60 minutes on Day 1, of each 3-week treatment cycle for a total of 6 cycles (18 weeks) or until progressive disease (PD), unacceptable toxicity or withdrawal for any other reason. After 6 cycles, participants received cilengitide 2000 mg once weekly along with cetuximab 250 mg/m^2 intravenous infusion until PD, unacceptable toxicity or withdrawal for any other reason.

	Description
Cilengitide 2000 mg Twice Weekly +Cetuximab+5-FU+Cisplatin	Cilengitide 2000 mg intravenous infusion over 60 minutes twice weekly along with cetuximab 250 mg/m^2 intravenous infusion (initial starting dose of 400 mg/m^2) once weekly, 5-fluorouracil (5-FU) 1000 mg/m^2 intravenous continuous infusion daily from Day 1 to 4 and cisplatin 100 mg/m^2 intravenous infusion over 60 minutes on Day 1, of each 3-week treatment cycle for a total of 6 cycles (18 weeks) or until PD, unacceptable toxicity or withdrawal for any other reason. After 6 cycles, participants received cilengitide 2000 mg once weekly along with cetuximab 250 mg/m^2 intravenous infusion until PD, unacceptable toxicity or withdrawal for any other reason.
Cetuximab+5-FU+Cisplatin	Cetuximab 250 mg/m^2 intravenous infusion (initial starting dose of 400 mg/m^2) once weekly along with 5-fluorouracil (5-FU) 1000 mg/m^2 intravenous continuous infusion daily from Day 1 to 4 and cisplatin 100 mg/m^2 intravenous infusion over 60 minutes on Day 1, of each 3-week treatment cycle for a total of 6 cycles (18 weeks) or until PD, unacceptable toxicity or withdrawal for any other reason. After 6 cycles, participants received cetuximab 250 mg/m^2 intravenous infusion until PD, unacceptable toxicity or withdrawal for any other reason.

Measured Values

	Cilengitide 2000 mg Once Weekly+Cetuximab +5-FU+Cisplatin	Cilengitide 2000 mg Twice Weekly+Cetuximab +5-FU+Cisplatin	Cetuximab+5-FU+Cisplatin
Number of Participants Analyzed	61	59	62
Safety - Number of Participants Experiencing Any Adverse Event [units: participants]	61	59	61

Reported Adverse Events

Time Frame	Time from first dose up to 28 days after last dose of study treatment, reported between day of first patient randomized, 01 October 2008, until cut off date, 03 September 2011
Additional Description	[Not specified]

Reporting Groups

	Description
Cilengitide 2000 mg Once Weekly +Cetuximab+5-FU+Cisplatin	Cilengitide 500 milligram (mg) intravenous infusion over 60 minutes, daily from Day 1 to 4 of the first week of each 3-week cycle, subsequently followed by cilengitide 2000 mg once weekly along with cetuximab 250 milligram per square meter (mg/m^2) intravenous infusion (initial starting dose of 400 mg/m^2) once weekly, 5-fluorouracil (5-FU) 1000 mg/m^2 intravenous continuous infusion daily from Day 1 to 4 and cisplatin 100 mg/m^2 intravenous infusion over 60 minutes on Day 1, of each 3-week treatment cycle for a total of 6 cycles (18 weeks) or until progressive disease (PD), unacceptable toxicity or withdrawal for any other reason. After 6 cycles, participants received cilengitide 2000 mg once weekly along with cetuximab 250 mg/m^2 intravenous infusion until PD, unacceptable toxicity or withdrawal for any other reason.
Cilengitide 2000 mg Twice Weekly +Cetuximab+5-FU+Cisplatin	Cilengitide 2000 mg intravenous infusion over 60 minutes twice weekly along with cetuximab 250 mg/m^2 intravenous infusion (initial starting dose of 400 mg/m^2) once weekly, 5-fluorouracil (5-FU) 1000 mg/m^2 intravenous continuous infusion daily from Day 1 to 4 and cisplatin 100 mg/m^2 intravenous infusion over 60 minutes on Day 1, of each 3-week treatment cycle for a total of 6 cycles (18 weeks) or until PD, unacceptable toxicity or withdrawal for any other reason. After 6 cycles, participants received cilengitide 2000 mg once weekly along with cetuximab 250 mg/m^2 intravenous infusion until PD, unacceptable toxicity or withdrawal for any other reason.
Cetuximab+5-FU+Cisplatin	Cetuximab 250 mg/m^2 intravenous infusion (initial starting dose of 400 mg/m^2) once weekly along with 5-fluorouracil (5-FU) 1000 mg/m^2 intravenous continuous infusion daily from Day 1 to 4 and cisplatin 100 mg/m^2 intravenous infusion over 60 minutes on Day 1, of each 3-week treatment cycle for a total of 6 cycles (18 weeks) or until PD, unacceptable toxicity or withdrawal for any other reason. After 6 cycles, participants received cetuximab 250 mg/m^2 intravenous infusion until PD, unacceptable toxicity or withdrawal for any other reason.

Serious Adverse Events

	Cilengitide 2000 mg Once Weekly+Cetuximab +5-FU+Cisplatin		Cilengitide 2000 mg Twice Weekly+Cetuximab +5-FU+Cisplatin		Cetuximab+5-FU+Cisplatin	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Total	41/61 (67.21%)		45/59 (76.27%)		44/62 (70.97%)	
Blood and lymphatic system disorders						
Anaemia [A] *	0/61 (0%)	0	1/59 (1.69%)	1	4/62 (6.45%)	4
Febrile Neutropenia [A] *	0/61 (0%)	0	4/59 (6.78%)	5	6/62 (9.68%)	6
Leukopenia [A] *	0/61 (0%)	0	2/59 (3.39%)	3	1/62 (1.61%)	1
Lymphopenia [A] *	0/61 (0%)	0	0/59 (0%)	0	1/62 (1.61%)	1

	Cilengitide 2000 mg Once Weekly+Cetuximab +5-FU+Cisplatin		Cilengitide 2000 mg Twice Weekly+Cetuximab +5-FU+Cisplatin		Cetuximab+5-FU+Cisplatin	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Neutropenia [A] *	3/61 (4.92%)	3	6/59 (10.17%)	7	5/62 (8.06%)	7
Pancytopenia [A] *	0/61 (0%)	0	0/59 (0%)	0	1/62 (1.61%)	1
Thrombocytopenia [A] *	2/61 (3.28%)	2	1/59 (1.69%)	1	1/62 (1.61%)	2
Cardiac disorders						
Acute Myocardial Infarction [A] *	0/61 (0%)	0	1/59 (1.69%)	1	0/62 (0%)	0
Atrial Fibrillation [A] *	0/61 (0%)	0	1/59 (1.69%)	1	0/62 (0%)	0
Atrial Flutter [A] *	0/61 (0%)	0	1/59 (1.69%)	1	0/62 (0%)	0
Cardiac Arrest [A] *	0/61 (0%)	0	1/59 (1.69%)	1	0/62 (0%)	0
Cardiac Failure Congestive [A] *	0/61 (0%)	0	0/59 (0%)	0	1/62 (1.61%)	1
Myocardial Infarction [A] *	1/61 (1.64%)	1	0/59 (0%)	0	1/62 (1.61%)	1
Pericarditis [A] *	0/61 (0%)	0	0/59 (0%)	0	1/62 (1.61%)	1
Ear and labyrinth disorders						
Deafness [A] *	1/61 (1.64%)	1	0/59 (0%)	0	0/62 (0%)	0
Hypoacusis [A] *	1/61 (1.64%)	2	0/59 (0%)	0	0/62 (0%)	0
Ototoxicity [A] *	1/61 (1.64%)	1	0/59 (0%)	0	0/62 (0%)	0
Vertigo [A] *	0/61 (0%)	0	0/59 (0%)	0	1/62 (1.61%)	1
Endocrine disorders						
Adrenal Insufficiency [A] *	0/61 (0%)	0	0/59 (0%)	0	1/62 (1.61%)	1
Hypothyroidism [A] *	0/61 (0%)	0	1/59 (1.69%)	1	0/62 (0%)	0
Eye disorders						
Retinal Artery Occlusion [A] *	1/61 (1.64%)	1	0/59 (0%)	0	0/62 (0%)	0

	Cilengitide 2000 mg Once Weekly+Cetuximab +5-FU+Cisplatin		Cilengitide 2000 mg Twice Weekly+Cetuximab +5-FU+Cisplatin		Cetuximab+5-FU+Cisplatin	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Retinal Artery Thrombosis [A] *	0/61 (0%)	0	1/59 (1.69%)	1	0/62 (0%)	0
Visual Acuity Reduced [A] *	1/61 (1.64%)	1	0/59 (0%)	0	0/62 (0%)	0
Gastrointestinal disorders						
Abdominal Pain [A] *	2/61 (3.28%)	3	0/59 (0%)	0	0/62 (0%)	0
Diarrhoea [A] *	1/61 (1.64%)	1	3/59 (5.08%)	4	2/62 (3.23%)	2
Duodenal Perforation [A] *	1/61 (1.64%)	1	0/59 (0%)	0	0/62 (0%)	0
Dysphagia [A] *	1/61 (1.64%)	1	0/59 (0%)	0	1/62 (1.61%)	1
Gastric Ulcer [A] *	0/61 (0%)	0	0/59 (0%)	0	1/62 (1.61%)	1
Gastrointestinal Haemorrhage [A] *	1/61 (1.64%)	1	0/59 (0%)	0	1/62 (1.61%)	1
Large Intestine Perforation [A] *	0/61 (0%)	0	1/59 (1.69%)	1	0/62 (0%)	0
Lower Gastrointestinal Haemorrhage [A] *	0/61 (0%)	0	0/59 (0%)	0	1/62 (1.61%)	1
Nausea [A] *	0/61 (0%)	0	2/59 (3.39%)	2	2/62 (3.23%)	2
Neutropenic Colitis [A] *	0/61 (0%)	0	0/59 (0%)	0	1/62 (1.61%)	1
Oesophageal Perforation [A] *	0/61 (0%)	0	1/59 (1.69%)	1	0/62 (0%)	0
Rectal Haemorrhage [A] *	0/61 (0%)	0	0/59 (0%)	0	1/62 (1.61%)	1
Stomatitis [A] *	1/61 (1.64%)	1	4/59 (6.78%)	6	5/62 (8.06%)	5
Tongue Necrosis [A] *	0/61 (0%)	0	0/59 (0%)	0	1/62 (1.61%)	1
Vomiting [A] *	2/61 (3.28%)	2	0/59 (0%)	0	5/62 (8.06%)	5
General disorders						
Asthenia [A] *	1/61 (1.64%)	1	0/59 (0%)	0	1/62 (1.61%)	1
Catheter Site Inflammation [A] *	0/61 (0%)	0	1/59 (1.69%)	1	0/62 (0%)	0

	Cilengitide 2000 mg Once Weekly+Cetuximab +5-FU+Cisplatin		Cilengitide 2000 mg Twice Weekly+Cetuximab +5-FU+Cisplatin		Cetuximab+5-FU+Cisplatin	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Death [A] *	2/61 (3.28%)	2	0/59 (0%)	0	0/62 (0%)	0
Device Dislocation [A] *	0/61 (0%)	0	2/59 (3.39%)	3	0/62 (0%)	0
Device Leakage [A] *	0/61 (0%)	0	1/59 (1.69%)	1	0/62 (0%)	0
Face Oedema [A] *	0/61 (0%)	0	1/59 (1.69%)	1	1/62 (1.61%)	1
Fatigue [A] *	0/61 (0%)	0	1/59 (1.69%)	1	3/62 (4.84%)	3
General Physical Health Deterioration [A] *	3/61 (4.92%)	3	4/59 (6.78%)	4	2/62 (3.23%)	3
Hyperpyrexia [A] *	0/61 (0%)	0	0/59 (0%)	0	1/62 (1.61%)	1
Mucosal Inflammation [A] *	0/61 (0%)	0	0/59 (0%)	0	1/62 (1.61%)	1
Oedema Peripheral [A] *	0/61 (0%)	0	1/59 (1.69%)	1	0/62 (0%)	0
Pain [A] *	1/61 (1.64%)	1	0/59 (0%)	0	1/62 (1.61%)	1
Performance Status Decreased [A] *	0/61 (0%)	0	0/59 (0%)	0	1/62 (1.61%)	1
Pyrexia [A] *	2/61 (3.28%)	2	4/59 (6.78%)	4	2/62 (3.23%)	2
Sudden Death [A] *	0/61 (0%)	0	1/59 (1.69%)	1	0/62 (0%)	0
Thrombosis In Device [A] *	1/61 (1.64%)	1	1/59 (1.69%)	1	0/62 (0%)	0
Hepatobiliary disorders						
Acute Hepatic Failure [A] *	0/61 (0%)	0	1/59 (1.69%)	1	0/62 (0%)	0
Cholelithiasis [A] *	1/61 (1.64%)	1	0/59 (0%)	0	0/62 (0%)	0
Hepatic Failure [A] *	0/61 (0%)	0	0/59 (0%)	0	1/62 (1.61%)	1
Immune system disorders						
Anaphylactic Reaction [A] *	0/61 (0%)	0	1/59 (1.69%)	1	0/62 (0%)	0
Drug Hypersensitivity [A] *	2/61 (3.28%)	2	2/59 (3.39%)	2	0/62 (0%)	0

	Cilengitide 2000 mg Once Weekly+Cetuximab +5-FU+Cisplatin		Cilengitide 2000 mg Twice Weekly+Cetuximab +5-FU+Cisplatin		Cetuximab+5-FU+Cisplatin	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Hypersensitivity [A] *	1/61 (1.64%)	1	0/59 (0%)	0	0/62 (0%)	0
Infections and infestations						
Catheter Site Infection [A] *	0/61 (0%)	0	1/59 (1.69%)	1	0/62 (0%)	0
Dermatitis Infected [A] *	0/61 (0%)	0	0/59 (0%)	0	1/62 (1.61%)	1
Device Related Infection [A] *	2/61 (3.28%)	2	0/59 (0%)	0	1/62 (1.61%)	1
Enterocolitis Infectious [A] *	0/61 (0%)	0	1/59 (1.69%)	1	0/62 (0%)	0
Escherichia Bacteraemia [A] *	0/61 (0%)	0	0/59 (0%)	0	1/62 (1.61%)	2
Escherichia Sepsis [A] *	0/61 (0%)	0	1/59 (1.69%)	1	0/62 (0%)	0
Gastroenteritis [A] *	1/61 (1.64%)	1	2/59 (3.39%)	2	0/62 (0%)	0
Infection [A] *	0/61 (0%)	0	0/59 (0%)	0	1/62 (1.61%)	1
Oral Fungal Infection [A] *	0/61 (0%)	0	1/59 (1.69%)	1	0/62 (0%)	0
Parotitis [A] *	0/61 (0%)	0	0/59 (0%)	0	1/62 (1.61%)	1
Pneumonia [A] *	5/61 (8.2%)	5	5/59 (8.47%)	5	5/62 (8.06%)	6
Postoperative Wound Infection [A] *	1/61 (1.64%)	1	0/59 (0%)	0	0/62 (0%)	0
Pulmonary Sepsis [A] *	0/61 (0%)	0	1/59 (1.69%)	2	0/62 (0%)	0
Respiratory Tract Infection [A] *	0/61 (0%)	0	1/59 (1.69%)	2	0/62 (0%)	0
Sepsis [A] *	3/61 (4.92%)	4	0/59 (0%)	0	2/62 (3.23%)	2
Skin Infection [A] *	0/61 (0%)	0	1/59 (1.69%)	1	0/62 (0%)	0
Staphylococcal Infection [A] *	0/61 (0%)	0	1/59 (1.69%)	1	0/62 (0%)	0
Staphylococcal Sepsis [A] *	0/61 (0%)	0	1/59 (1.69%)	1	0/62 (0%)	0
Wound Infection [A] *	0/61 (0%)	0	0/59 (0%)	0	1/62 (1.61%)	1

	Cilengitide 2000 mg Once Weekly+Cetuximab +5-FU+Cisplatin		Cilengitide 2000 mg Twice Weekly+Cetuximab +5-FU+Cisplatin		Cetuximab+5-FU+Cisplatin	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Injury, poisoning and procedural complications						
Alcohol Poisoning [A] *	0/61 (0%)	0	1/59 (1.69%)	1	0/62 (0%)	0
Ankle Fracture [A] *	1/61 (1.64%)	1	0/59 (0%)	0	0/62 (0%)	0
Facial Bones Fracture [A] *	0/61 (0%)	0	0/59 (0%)	0	1/62 (1.61%)	1
Gastrostomy Failure [A] *	0/61 (0%)	0	1/59 (1.69%)	1	0/62 (0%)	0
Toxicity To Various Agents [A] *	1/61 (1.64%)	1	1/59 (1.69%)	1	0/62 (0%)	0
Investigations						
Blood Amylase Increased [A] *	1/61 (1.64%)	1	0/59 (0%)	0	0/62 (0%)	0
Blood Creatine Increased [A] *	0/61 (0%)	0	0/59 (0%)	0	1/62 (1.61%)	1
Blood Creatinine Increased [A] *	0/61 (0%)	0	1/59 (1.69%)	2	2/62 (3.23%)	2
Glomerular Filtration Rate Decreased [A] *	0/61 (0%)	0	1/59 (1.69%)	1	0/62 (0%)	0
Weight Decreased [A] *	1/61 (1.64%)	1	0/59 (0%)	0	0/62 (0%)	0
Metabolism and nutrition disorders						
Decreased Appetite [A] *	0/61 (0%)	0	0/59 (0%)	0	1/62 (1.61%)	2
Dehydration [A] *	3/61 (4.92%)	6	1/59 (1.69%)	2	9/62 (14.52%)	9
Hyperglycaemia [A] *	0/61 (0%)	0	0/59 (0%)	0	2/62 (3.23%)	2
Hypocalcaemia [A] *	0/61 (0%)	0	2/59 (3.39%)	3	1/62 (1.61%)	1
Hypokalaemia [A] *	1/61 (1.64%)	1	6/59 (10.17%)	11	2/62 (3.23%)	2
Hypomagnesaemia [A] *	0/61 (0%)	0	1/59 (1.69%)	1	0/62 (0%)	0
Hyponatraemia [A] *	1/61 (1.64%)	1	4/59 (6.78%)	5	0/62 (0%)	0
Hypophagia [A] *	0/61 (0%)	0	1/59 (1.69%)	1	0/62 (0%)	0

	Cilengitide 2000 mg Once Weekly+Cetuximab +5-FU+Cisplatin		Cilengitide 2000 mg Twice Weekly+Cetuximab +5-FU+Cisplatin		Cetuximab+5-FU+Cisplatin	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Musculoskeletal and connective tissue disorders						
Pain In Jaw [A] *	0/61 (0%)	0	0/59 (0%)	0	1/62 (1.61%)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Infected Neoplasm [A] *	0/61 (0%)	0	0/59 (0%)	0	1/62 (1.61%)	1
Paraneoplastic Syndrome [A] *	0/61 (0%)	0	0/59 (0%)	0	1/62 (1.61%)	2
Tumour Haemorrhage [A] *	0/61 (0%)	0	0/59 (0%)	0	2/62 (3.23%)	2
Nervous system disorders						
Cerebral Infarction [A] *	0/61 (0%)	0	0/59 (0%)	0	1/62 (1.61%)	1
Cerebrovascular Accident [A] *	0/61 (0%)	0	1/59 (1.69%)	1	0/62 (0%)	0
Depressed Level Of Consciousness [A] *	0/61 (0%)	0	0/59 (0%)	0	1/62 (1.61%)	1
Dizziness [A] *	0/61 (0%)	0	1/59 (1.69%)	1	0/62 (0%)	0
Syncope [A] *	3/61 (4.92%)	3	3/59 (5.08%)	3	1/62 (1.61%)	1
Psychiatric disorders						
Suicide Attempt [A] *	0/61 (0%)	0	1/59 (1.69%)	1	0/62 (0%)	0
Renal and urinary disorders						
Renal Failure [A] *	0/61 (0%)	0	2/59 (3.39%)	2	1/62 (1.61%)	1
Renal Failure Acute [A] *	1/61 (1.64%)	1	0/59 (0%)	0	1/62 (1.61%)	1
Renal Impairment [A] *	0/61 (0%)	0	1/59 (1.69%)	1	0/62 (0%)	0
Respiratory, thoracic and mediastinal disorders						
Chronic Obstructive Pulmonary Disease [A] *	0/61 (0%)	0	1/59 (1.69%)	1	1/62 (1.61%)	1
Dyspnoea [A] *	2/61 (3.28%)	4	1/59 (1.69%)	1	1/62 (1.61%)	1

	Cilengitide 2000 mg Once Weekly+Cetuximab +5-FU+Cisplatin		Cilengitide 2000 mg Twice Weekly+Cetuximab +5-FU+Cisplatin		Cetuximab+5-FU+Cisplatin	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Hypoxia [A] *	1/61 (1.64%)	1	1/59 (1.69%)	1	1/62 (1.61%)	1
Interstitial Lung Disease [A] *	0/61 (0%)	0	1/59 (1.69%)	1	0/62 (0%)	0
Lung Infiltration [A] *	0/61 (0%)	0	1/59 (1.69%)	1	0/62 (0%)	0
Organising Pneumonia [A] *	0/61 (0%)	0	0/59 (0%)	0	1/62 (1.61%)	1
Pneumonia Aspiration [A] *	1/61 (1.64%)	1	0/59 (0%)	0	0/62 (0%)	0
Pneumonitis [A] *	1/61 (1.64%)	1	0/59 (0%)	0	0/62 (0%)	0
Pulmonary Artery Thrombosis [A] *	1/61 (1.64%)	1	0/59 (0%)	0	1/62 (1.61%)	1
Pulmonary Embolism [A] *	4/61 (6.56%)	4	2/59 (3.39%)	2	1/62 (1.61%)	1
Pulmonary Haemorrhage [A] *	0/61 (0%)	0	0/59 (0%)	0	1/62 (1.61%)	1
Respiratory Failure [A] *	1/61 (1.64%)	1	1/59 (1.69%)	1	0/62 (0%)	0
Skin and subcutaneous tissue disorders						
Dermatitis Acneiform [A] *	0/61 (0%)	0	0/59 (0%)	0	1/62 (1.61%)	1
Vascular disorders						
Arterial Rupture [A] *	0/61 (0%)	0	1/59 (1.69%)	1	0/62 (0%)	0
Arteriosclerosis [A] *	1/61 (1.64%)	1	0/59 (0%)	0	0/62 (0%)	0
Arteriosclerosis Obliterans [A] *	0/61 (0%)	0	1/59 (1.69%)	1	0/62 (0%)	0
Axillary Vein Thrombosis [A] *	1/61 (1.64%)	2	0/59 (0%)	0	0/62 (0%)	0
Hypotension [A] *	3/61 (4.92%)	3	2/59 (3.39%)	2	1/62 (1.61%)	1
Jugular Vein Thrombosis [A] *	1/61 (1.64%)	1	0/59 (0%)	0	0/62 (0%)	0
Orthostatic Hypotension [A] *	0/61 (0%)	0	0/59 (0%)	0	1/62 (1.61%)	1
Phlebitis [A] *	0/61 (0%)	0	0/59 (0%)	0	1/62 (1.61%)	1

	Cilengitide 2000 mg Once Weekly+Cetuximab +5-FU+Cisplatin		Cilengitide 2000 mg Twice Weekly+Cetuximab +5-FU+Cisplatin		Cetuximab+5-FU+Cisplatin	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Thrombosis [A] *	1/61 (1.64%)	1	0/59 (0%)	0	1/62 (1.61%)	1

* 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: 5%

	Cilengitide 2000 mg Once Weekly+Cetuximab +5-FU+Cisplatin		Cilengitide 2000 mg Twice Weekly+Cetuximab +5-FU+Cisplatin		Cetuximab+5-FU+Cisplatin	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Total	61/61 (100%)		57/59 (96.61%)		61/62 (98.39%)	
Blood and lymphatic system disorders						
Anaemia [A] *	22/61 (36.07%)	57	16/59 (27.12%)	45	22/62 (35.48%)	65
Leukopenia [A] *	16/61 (26.23%)	38	15/59 (25.42%)	52	12/62 (19.35%)	39
Lymphopenia [A] *	5/61 (8.2%)	8	2/59 (3.39%)	6	3/62 (4.84%)	13
Neutropenia [A] *	28/61 (45.9%)	63	24/59 (40.68%)	108	29/62 (46.77%)	80
Normochromic Normocytic Anaemia [A] *	1/61 (1.64%)	6	3/59 (5.08%)	4	5/62 (8.06%)	5
Thrombocytopenia [A] *	9/61 (14.75%)	24	15/59 (25.42%)	33	14/62 (22.58%)	30
Cardiac disorders						
Palpitations [A] *	1/61 (1.64%)	1	0/59 (0%)	0	4/62 (6.45%)	7
Ear and labyrinth disorders						
Deafness [A] *	5/61 (8.2%)	6	3/59 (5.08%)	4	4/62 (6.45%)	4

	Cilengitide 2000 mg Once Weekly+Cetuximab +5-FU+Cisplatin		Cilengitide 2000 mg Twice Weekly+Cetuximab +5-FU+Cisplatin		Cetuximab+5-FU+Cisplatin	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Hypoacusis [A] *	0/61 (0%)	0	4/59 (6.78%)	4	1/62 (1.61%)	1
Tinnitus [A] *	3/61 (4.92%)	7	5/59 (8.47%)	9	4/62 (6.45%)	4
Vertigo [A] *	3/61 (4.92%)	3	5/59 (8.47%)	6	3/62 (4.84%)	9
Eye disorders						
Conjunctivitis [A] *	8/61 (13.11%)	9	3/59 (5.08%)	5	10/62 (16.13%)	13
Gastrointestinal disorders						
Abdominal Pain [A] *	7/61 (11.48%)	9	7/59 (11.86%)	9	1/62 (1.61%)	1
Abdominal Pain Upper [A] *	6/61 (9.84%)	9	5/59 (8.47%)	5	4/62 (6.45%)	6
Constipation [A] *	23/61 (37.7%)	43	22/59 (37.29%)	37	24/62 (38.71%)	36
Diarrhoea [A] *	23/61 (37.7%)	45	27/59 (45.76%)	60	24/62 (38.71%)	65
Dry Mouth [A] *	3/61 (4.92%)	3	2/59 (3.39%)	2	4/62 (6.45%)	4
Dyspepsia [A] *	6/61 (9.84%)	6	3/59 (5.08%)	4	11/62 (17.74%)	16
Dysphagia [A] *	5/61 (8.2%)	11	7/59 (11.86%)	10	8/62 (12.9%)	12
Gastritis [A] *	0/61 (0%)	0	3/59 (5.08%)	3	0/62 (0%)	0
Gastrooesophageal Reflux Disease [A] *	2/61 (3.28%)	2	0/59 (0%)	0	4/62 (6.45%)	5
Nausea [A] *	36/61 (59.02%)	98	31/59 (52.54%)	78	40/62 (64.52%)	137
Odynophagia [A] *	3/61 (4.92%)	3	0/59 (0%)	0	4/62 (6.45%)	4
Stomatitis [A] *	27/61 (44.26%)	85	28/59 (47.46%)	77	30/62 (48.39%)	83

	Cilengitide 2000 mg Once Weekly+Cetuximab +5-FU+Cisplatin		Cilengitide 2000 mg Twice Weekly+Cetuximab +5-FU+Cisplatin		Cetuximab+5-FU+Cisplatin	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Vomiting [A] *	28/61 (45.9%)	66	24/59 (40.68%)	55	28/62 (45.16%)	96
General disorders						
Asthenia [A] *	21/61 (34.43%)	80	7/59 (11.86%)	28	17/62 (27.42%)	61
Face Oedema [A] *	1/61 (1.64%)	1	3/59 (5.08%)	3	4/62 (6.45%)	4
Fatigue [A] *	20/61 (32.79%)	47	24/59 (40.68%)	62	24/62 (38.71%)	65
Oedema Peripheral [A] *	5/61 (8.2%)	13	11/59 (18.64%)	26	10/62 (16.13%)	17
Pyrexia [A] *	14/61 (22.95%)	23	13/59 (22.03%)	17	18/62 (29.03%)	39
Immune system disorders						
Drug Hypersensitivity [A] *	3/61 (4.92%)	3	2/59 (3.39%)	2	5/62 (8.06%)	5
Infections and infestations						
Device Related Infection [A] *	5/61 (8.2%)	6	3/59 (5.08%)	4	1/62 (1.61%)	1
Folliculitis [A] *	6/61 (9.84%)	10	6/59 (10.17%)	16	4/62 (6.45%)	8
Infection [A] *	2/61 (3.28%)	4	3/59 (5.08%)	3	3/62 (4.84%)	3
Nasopharyngitis [A] *	2/61 (3.28%)	2	4/59 (6.78%)	4	2/62 (3.23%)	4
Oral Candidiasis [A] *	4/61 (6.56%)	8	3/59 (5.08%)	4	1/62 (1.61%)	1
Oral Fungal Infection [A] *	0/61 (0%)	0	3/59 (5.08%)	4	3/62 (4.84%)	7
Paronychia [A] *	7/61 (11.48%)	10	4/59 (6.78%)	10	6/62 (9.68%)	11
Pneumonia [A] *	4/61 (6.56%)	4	5/59 (8.47%)	5	2/62 (3.23%)	2
Investigations						

	Cilengitide 2000 mg Once Weekly+Cetuximab +5-FU+Cisplatin		Cilengitide 2000 mg Twice Weekly+Cetuximab +5-FU+Cisplatin		Cetuximab+5-FU+Cisplatin	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Blood Creatinine Increased [A] *	6/61 (9.84%)	6	8/59 (13.56%)	18	7/62 (11.29%)	13
Haemoglobin Decreased [A] *	8/61 (13.11%)	39	9/59 (15.25%)	35	7/62 (11.29%)	22
Neutrophil Count Decreased [A] *	7/61 (11.48%)	26	3/59 (5.08%)	7	4/62 (6.45%)	11
Platelet Count Decreased [A] *	4/61 (6.56%)	14	5/59 (8.47%)	8	6/62 (9.68%)	19
Weight Decreased [A] *	12/61 (19.67%)	22	10/59 (16.95%)	12	12/62 (19.35%)	15
White Blood Cell Count Decreased [A] *	7/61 (11.48%)	32	2/59 (3.39%)	18	4/62 (6.45%)	19
Metabolism and nutrition disorders						
Decreased Appetite [A] *	20/61 (32.79%)	37	15/59 (25.42%)	42	18/62 (29.03%)	45
Dehydration [A] *	2/61 (3.28%)	3	3/59 (5.08%)	3	5/62 (8.06%)	5
Hyperglycaemia [A] *	1/61 (1.64%)	1	1/59 (1.69%)	2	5/62 (8.06%)	7
Hyperkalaemia [A] *	6/61 (9.84%)	6	3/59 (5.08%)	4	1/62 (1.61%)	2
Hypocalcaemia [A] *	6/61 (9.84%)	13	8/59 (13.56%)	25	9/62 (14.52%)	32
Hypokalaemia [A] *	19/61 (31.15%)	41	15/59 (25.42%)	50	15/62 (24.19%)	37
Hypomagnesaemia [A] *	17/61 (27.87%)	36	13/59 (22.03%)	55	14/62 (22.58%)	38
Hyponatraemia [A] *	7/61 (11.48%)	19	7/59 (11.86%)	21	4/62 (6.45%)	5
Musculoskeletal and connective tissue disorders						
Arthralgia [A] *	1/61 (1.64%)	1	5/59 (8.47%)	5	0/62 (0%)	0
Back Pain [A] *	4/61 (6.56%)	5	7/59 (11.86%)	7	3/62 (4.84%)	4
Muscle Spasms [A] *	1/61 (1.64%)	1	4/59 (6.78%)	4	4/62 (6.45%)	5

	Cilengitide 2000 mg Once Weekly+Cetuximab +5-FU+Cisplatin		Cilengitide 2000 mg Twice Weekly+Cetuximab +5-FU+Cisplatin		Cetuximab+5-FU+Cisplatin	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Neck Pain [A] *	4/61 (6.56%)	7	3/59 (5.08%)	4	2/62 (3.23%)	2
Pain In Extremity [A] *	2/61 (3.28%)	2	6/59 (10.17%)	8	4/62 (6.45%)	5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Tumour Pain [A] *	3/61 (4.92%)	5	6/59 (10.17%)	13	6/62 (9.68%)	11
Nervous system disorders						
Dizziness [A] *	8/61 (13.11%)	18	9/59 (15.25%)	20	6/62 (9.68%)	14
Dysgeusia [A] *	4/61 (6.56%)	5	2/59 (3.39%)	2	5/62 (8.06%)	6
Headache [A] *	8/61 (13.11%)	13	4/59 (6.78%)	4	5/62 (8.06%)	6
Neuropathy Peripheral [A] *	6/61 (9.84%)	14	1/59 (1.69%)	1	2/62 (3.23%)	4
Paraesthesia [A] *	6/61 (9.84%)	17	4/59 (6.78%)	7	5/62 (8.06%)	7
Peripheral Sensory Neuropathy [A] *	4/61 (6.56%)	10	7/59 (11.86%)	15	3/62 (4.84%)	12
Polyneuropathy [A] *	5/61 (8.2%)	5	2/59 (3.39%)	2	2/62 (3.23%)	4
Syncope [A] *	2/61 (3.28%)	2	3/59 (5.08%)	4	3/62 (4.84%)	4
Psychiatric disorders						
Anxiety [A] *	3/61 (4.92%)	3	1/59 (1.69%)	1	4/62 (6.45%)	4
Insomnia [A] *	4/61 (6.56%)	6	7/59 (11.86%)	8	6/62 (9.68%)	6
Renal and urinary disorders						
Dysuria [A] *	2/61 (3.28%)	2	3/59 (5.08%)	4	1/62 (1.61%)	3
Respiratory, thoracic and mediastinal disorders						
Cough [A] *	8/61 (13.11%)	14	12/59 (20.34%)	17	6/62 (9.68%)	10
Dysphonia [A] *	2/61 (3.28%)	4	2/59 (3.39%)	2	4/62 (6.45%)	8

	Cilengitide 2000 mg Once Weekly+Cetuximab +5-FU+Cisplatin		Cilengitide 2000 mg Twice Weekly+Cetuximab +5-FU+Cisplatin		Cetuximab+5-FU+Cisplatin	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Dyspnoea [A] *	8/61 (13.11%)	17	9/59 (15.25%)	11	10/62 (16.13%)	12
Epistaxis [A] *	6/61 (9.84%)	7	9/59 (15.25%)	13	4/62 (6.45%)	10
Oropharyngeal Pain [A] *	3/61 (4.92%)	4	5/59 (8.47%)	8	6/62 (9.68%)	8
Skin and subcutaneous tissue disorders						
Acne [A] *	6/61 (9.84%)	8	4/59 (6.78%)	8	5/62 (8.06%)	11
Alopecia [A] *	12/61 (19.67%)	19	9/59 (15.25%)	13	11/62 (17.74%)	12
Dermatitis Acneiform [A] *	11/61 (18.03%)	29	11/59 (18.64%)	30	11/62 (17.74%)	34
Dry Skin [A] *	15/61 (24.59%)	35	13/59 (22.03%)	19	11/62 (17.74%)	18
Erythema [A] *	9/61 (14.75%)	22	2/59 (3.39%)	2	5/62 (8.06%)	5
Exfoliative Rash [A] *	4/61 (6.56%)	27	3/59 (5.08%)	6	1/62 (1.61%)	1
Nail Disorder [A] *	3/61 (4.92%)	6	7/59 (11.86%)	13	1/62 (1.61%)	4
Palmar-Plantar Erythrodysaesthesia Syndrome [A] *	5/61 (8.2%)	11	3/59 (5.08%)	6	2/62 (3.23%)	3
Pruritus [A] *	8/61 (13.11%)	11	3/59 (5.08%)	8	3/62 (4.84%)	6
Rash [A] *	22/61 (36.07%)	54	22/59 (37.29%)	99	27/62 (43.55%)	91
Skin Fissures [A] *	10/61 (16.39%)	32	9/59 (15.25%)	19	12/62 (19.35%)	22
Vascular disorders						
Hypertension [A] *	7/61 (11.48%)	11	6/59 (10.17%)	11	8/62 (12.9%)	14
Hypotension [A] *	6/61 (9.84%)	8	8/59 (13.56%)	11	4/62 (6.45%)	7

	Cilengitide 2000 mg Once Weekly+Cetuximab +5-FU+Cisplatin		Cilengitide 2000 mg Twice Weekly+Cetuximab +5-FU+Cisplatin		Cetuximab+5-FU+Cisplatin	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Phlebitis [A] *	2/61 (3.28%)	2	3/59 (5.08%)	4	3/62 (4.84%)	3

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

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

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

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

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