ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: 07/28/2014

ClinicalTrials.gov ID: NCT01040832

Study Identification

Unique Protocol ID:	EMR 200068-006
Brief Title:	EMD 1201081 in Combination With Cetuximab in Second-Line Cetuximab-Naïve Subjects With Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck
Official Title:	A Phase II, Open-label, 1:1 Randomized, Controlled Trial Exploring the Efficacy of EMD 1201081 in Combination With Cetuximab in Second-Line Cetuximab-Naïve Subjects With Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (R/M SCCHN)
Secondary IDs:	

Study Status

Record Verification:	July 2014
Overall Status:	Completed
Study Start:	December 2009
Primary Completion:	January 2012 [Actual]
Study Completion:	

Sponsor/Collaborators

Sponsor:	EMD Serono
Responsible Party:	Sponsor
Collaborators:	

Oversight

FDA Regulated?:	Yes
Applicable Trial?:	Section 801 Clinical Trial? Yes Delayed Posting? No
IND/IDE Protocol?:	Yes
IND/IDE Information:	Grantor: CDER IND/IDE Number: 102,129 Serial Number: Has Expanded Access? No
Review Board:	Approval Status: Approved Board Name: Federal Agency for Medicines and Healthcare Products Board Affiliation: No Affiliation Phone: +32 9 332 26 88 Email:
Data Monitoring?:	Yes
Plan to Share Data?:	
Oversight Authorities:	United States: Food and Drug Administration United Kingdom: Medicines and Healthcare Products Regulatory Agency Belgium: Federal Agency for Medicinal Products and Health Products

Study Description

Brief Summary: The purpose of this study is to determine if EMD 1201081 in combination with cetuximab is more efficient than cetuximab alone to control the cancer.

EMD 1201081 is an immune modulatory oligonucleotide (IMO) containing phosphorothioate oligodeoxynucleotide and acts as an agonist of Toll-like receptor 9 (TLR9).

EMD 1201081 has been studied in six clinical trials in over 170 subjects either as a monotherapy or in combination with chemotherapeutic agents or targeted therapies. Two studies have been conducted in healthy volunteers. In the other five studies, subjects with advanced solid tumors, renal cell carcinoma, non-small cell lung cancer and colorectal cancer have been treated with EMD 1201081. Two studies are still ongoing. Future clinical development of EMD 1201081 will focus on colorectal cancer (CRC) and squamous cell cancer of the head and neck (SCCHN).

In this Phase 2 study, subjects with recurrent or metastatic squamous cell cancer of the head and neck (R/M SCCHN), will be treated with cetuximab plus EMD 1201081 or cetuximab alone. The study will be conducted as a multicenter study in several European Union (EU) member states and the Unites States.

EMD 1201081 in combination with cetuximab will be evaluated for antitumor activity in subjects by examining its effects on accepted clinical endpoints. Progression-free survival (PFS) will be evaluated in subjects treated with EMD 1201081 plus

cetuximab compared to cetuximab alone in cetuximab-naïve subjects with R/M SCCHN who have progressed on a cytotoxic therapy.

Cetuximab, approved in colorectal cancer and SCCHN in combination with platinum-based chemotherapy and SCCHN in combination with radiotherapy in the EU, will be provided as investigational medicinal product (IMP) in this study. Commercially available Cetuximab will be provided in the United States.

Detailed Description:

Conditions

Conditions: Squamous Cell Carcinoma of the Head and Neck Cancer

Keywords: Head and Neck Cancer
Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck Cancer
Cetuximab
EMD 1201081

Study Design

Study Type: Interventional

Primary Purpose: Treatment

Study Phase: Phase 2

Intervention Model: Parallel Assignment

Number of Arms: 2

Masking: Open Label

Allocation: Randomized

Endpoint Classification: Safety/Efficacy Study

Enrollment: 107 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Cetuximab plus EMD 1201081	Drug: Cetuximab Cetuximab weekly (initial dose 400 milligram per square meter [mg/m^2] over 120 minutes followed by 250 mg/m^2 intravenous infusion over 60 minutes) will be administered in 3-week treatment cycle until disease progression. The total treatment period will be approximately 18 months. Other Names:

Arms	Assigned Interventions
	• Erbitux® Drug: EMD 1201081 EMD 1201081 weekly (0.32 milligram per kilogram [mg/kg] by subcutaneous injection) will be administered in 3-week treatment cycle until disease progression. Subjects who will discontinue cetuximab due to toxicity in cetuximab monotherapy, could continue to receive EMD 1201081 monotherapy until disease progression. The total treatment period will be approximately 18 months. Other Names: • IMO-2055
Active Comparator: Cetuximab monotherapy	Drug: Cetuximab Cetuximab weekly (initial dose 400 milligram per square meter [mg/m^2] over 120 minutes followed by 250 mg/m^2 intravenous infusion over 60 minutes) will be administered in 3-week treatment cycle until disease progression. The total treatment period will be approximately 18 months. Other Names: • Erbitux®

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age:

Gender: Both

Accepts Healthy Volunteers?: No

Criteria: Inclusion Criteria:

- Signed and dated written informed consent prior to any trial-specific procedure
- Male or female subjects age greater than or equal to (>=) 18 years with R/M SCCHN
- Histologically confirmed R/M SCCHN, documented in the medical record
- History of progressing disease on a first-line cytotoxic chemotherapy regimen for R/M SCCHN, such as 5-fluorouracil (FU) plus cisplatin, or taxanes. (A history of chemotherapy or radiotherapy for localized disease was not considered a first-line regimen)
- The subject is suited for systemic therapy in the opinion of the Investigator
- At least one radiographically documented lesion measurable according to response evaluation criteria in solid tumors (RECIST) 1.0. All target lesions are to be measurable (that is, the lesion must be adequately measurable in at least one

dimension; longest diameter to be recorded as >= 2 centimeter (cm) by conventional techniques or >= 1 centimeter (cm) by spiral computed tomography [CT] scan). Target lesions are to be selected from the required protocol imaging. If the sole site of measurable disease is in a prior radiation field, there has to be unequivocal evidence of progression at >= 8 weeks since the completion of radiation or a positive biopsy
- Eastern cooperative oncology group performance status (ECOG PS) of 0 or 1
- If female, either post-menopausal, surgically sterile, or having a negative urine or serum pregnancy test (beta-human chorionic gonadotropin [beta-HCG]) at screening and practicing medically accepted contraception. If male, practicing contraception if the risk of conception exists. For relevant subjects, the duration of contraception should be 1 week prior to the start of therapy through 4 weeks after receipt of trial therapy
- Recovered from previous toxicities of prior cytotoxic regimen to common terminology criteria of adverse events (CTCAE) Grade 1 (with the exception of alopecia)
- Hemoglobin >= 9 gram per deciliter (g/dL) without transfusion support; no transfusion within 7 days prior to screening)
- Neutrophils >= 1.5 * 10^9 per liter
- Platelets >= 100 * 10^9 per liter
- Prothrombin time/partial thromboplastin time (PT/PTT) less than or equal to (=<) 1.5 times the upper limit of normal (ULN) for the site, unless there is therapeutic anti-coagulation
- Serum creatinine =< 1.5 times the ULN for the site
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) =< 3 times the ULN for the site
- Be willing and able to comply with the protocol procedures for the duration of the trial

Exclusion Criteria:

- History of prior exposure to cetuximab or panitumumab or any other approved or investigational anti-epidermal growth factor receptor (EGFR) agents
- Undifferentiated nasopharyngeal carcinoma
- Chemotherapy, radiotherapy or any investigational agents within 4 weeks prior to first dose of study drug
- Major surgical or planned procedure within 30 days prior to first dose of trial medication (isolated biopsies are not considered major surgical procedures)
- Active malignancy other than SCCHN, non-metastatic basal cell or squamous cell carcinoma of the skin, or second primary SCCHN
- Impaired cardiac function (for example, left ventricular ejection fraction less than [<] 45 percent defined by echocardiograph or other study), history of uncontrolled serious arrhythmia, unstable angina pectoris, congestive heart failure (new york heart association [NYHA] Grade III and IV), myocardial infarction within the last 12 months prior to trial entry, or signs of pericardial effusion
- Hypertension uncontrolled by standard pharmacologic therapies
- History of diagnosed interstitial lung disease
- Subject requires systemic anti-coagulation (example, warfarin greater than [>] 10 milligram per day [mg/day])
- Pregnancy or breastfeeding
- Legal incapacity or limited legal capacity
- Significant medical or psychiatric disease which makes the trial inappropriate in the Investigator's opinion
- Any brain metastasis and/or leptomeningeal disease (known or suspected)
- Significant pre-existing immune deficiency, such as infection of human immuno-deficiency virus (HIV) (documented or known)
- Clinically significant ongoing infection
- Known hypersensitivity to the trial treatments

- Signs and symptoms suggestive of transmissible spongiform encephalopathy, or family members who suffer from such disease
- Other significant disease that in the Investigator's opinion would exclude the subject from the trial

Contacts/Locations

Study Officials: Philip Breitfeld, MD
Study Director
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Locations: United States, Kentucky
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Lexington, Kentucky, United States

United States, Massachusetts
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Boston, Massachusetts, United States

United States, New York
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Research Site
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Hungary
Research Site
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Research Site
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References

Citations: [Study Results] Ruzsa A, Sen M, Evans M, Lee LW, Hideghety K, Rottey S, Klimak P, Holeckova P, Fayette J, Csoszi T, Erfan J, Forssmann U, Goddemeier T, Bexon A, Nutting C; NA EMD 1201081 Study Group. Phase 2, open-label, 1:1 randomized controlled trial exploring the efficacy of EMD 1201081 in combination with cetuximab in second-line cetuximab-naïve patients with recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN). Invest New Drugs. 2014 Dec;32(6):1278-84. doi: 10.1007/s10637-014-0117-2. Epub 2014 Jun 4. PubMed 24894651

Links: URL: http://www.cancer.gov/
Description Related Info

Study Data/Documents:

Study Results

Participant Flow

Recruitment Details	First participant enrolled: 17 Dec 2009; Last participant signed informed consent: 15 Aug 2011; Clinical data cut-off: 11 Jan 2012.
Pre-Assignment Details	Of the 123 participants, 106 were randomized and 17 were screen failures (12 did not meet all eligibility criteria, 1 experienced progressive disease, 3 had unspecified reasons and data on 1 participant was missing). One participant who was not randomized but received cetuximab+EMD 1201081, was included in the safety population (107 participants).

Reporting Groups

	Description
Cetuximab Plus EMD 1201081	Cetuximab weekly (initial dose 400 milligram per square meter [mg/m^2] over 120 minutes followed by 250 mg/m^2 intravenous infusion over 60 minutes) and EMD 1201081 weekly (0.32 milligram per kilogram [mg/kg] by subcutaneous injection) was administered in 3-week treatment cycle until disease progression. Participants who had discontinued cetuximab due to toxicity in cetuximab monotherapy arm, continued to receive EMD 1201081 monotherapy until disease progression or participant elected to withdraw from the trial. The total treatment period was approximately 18 months.
Cetuximab Monotherapy	Cetuximab weekly (initial dose 400 mg/m^2 over 120 minutes followed by 250 mg/m^2 intravenous infusion over 60 minutes) was administered in 3-week treatment cycle until disease progression. Participants who had discontinued cetuximab due to toxicity of cetuximab monotherapy, continued to receive EMD 1201081 monotherapy until disease progression or participant elected to withdraw from the trial. The total treatment period was approximately 18 months.

Overall Study

	Cetuximab Plus EMD 1201081	Cetuximab Monotherapy
Started	54 [1]	53
Completed	8	16
Not Completed	46	37
Adverse Event	4	5
Death	4	6
Withdrawal by Subject	2	3
Progressive disease	32	17
Symptomatic deterioration	2	5
Unspecified	2	1

[1] One participant was treated with study drug 'Cetuximab Plus EMD 1201081' but was not randomized

Baseline Characteristics

Analysis Population Description

Intent-to-treat (ITT) population included all the randomized participants who had received study treatment.

Reporting Groups

	Description
Cetuximab Plus EMD 1201081	Cetuximab weekly (initial dose 400 milligram per square meter [mg/m^2] over 120 minutes followed by 250 mg/m^2 intravenous infusion over 60 minutes) and EMD 1201081 weekly (0.32 milligram per kilogram [mg/kg] by subcutaneous injection) was administered in 3-week treatment cycle until disease progression. Participants who had discontinued cetuximab due to toxicity in cetuximab monotherapy arm, continued to receive EMD 1201081 monotherapy until disease progression or participant elected to withdraw from the trial. The total treatment period was approximately 18 months.
Cetuximab Monotherapy	Cetuximab weekly (initial dose 400 mg/m^2 over 120 minutes followed by 250 mg/m^2 intravenous infusion over 60 minutes) was administered in 3-week treatment cycle until disease progression. Participants who had discontinued cetuximab due to toxicity of cetuximab monotherapy, continued to receive EMD 1201081 monotherapy until disease progression or participant elected to withdraw from the trial. The total treatment period was approximately 18 months.

Baseline Measures

	Cetuximab Plus EMD 1201081	Cetuximab Monotherapy	Total
Number of Participants	53	53	106
Age, Continuous [units: years] Mean (Standard Deviation)	56.8 (7.03)	56.8 (10.03)	56.8 (8.62)
Gender, Male/Female [units: participants]			
Female	8	8	16
Male	45	45	90

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Progression-free Survival (PFS) Time: Independent Read 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 were censored on the date of last tumor assessment.
Time Frame	Every 6 weeks until disease progression, death or last tumor assessment, reported between day of first participant randomized, that is, 17 Dec 2009 until cut-off date (11 Jan 2012)
Safety Issue?	No

Analysis Population Description

ITT population included all the randomized participants who had received study treatment.

Reporting Groups

	Description
Cetuximab Plus EMD 1201081	Cetuximab weekly (initial dose 400 milligram per square meter [mg/m^2] over 120 minutes followed by 250 mg/m^2 intravenous infusion over 60 minutes) and EMD 1201081 weekly (0.32 milligram per kilogram [mg/kg] by subcutaneous injection) was administered in 3-week treatment cycle until disease progression. Participants who had discontinued cetuximab due to toxicity in cetuximab monotherapy arm, continued to receive EMD 1201081 monotherapy until disease progression or participant elected to withdraw from the trial. The total treatment period was approximately 18 months.

	Description
Cetuximab Monotherapy	Cetuximab weekly (initial dose 400 mg/m^2 over 120 minutes followed by 250 mg/m^2 intravenous infusion over 60 minutes) was administered in 3-week treatment cycle until disease progression. Participants who had discontinued cetuximab due to toxicity of cetuximab monotherapy, continued to receive EMD 1201081 monotherapy until disease progression or participant elected to withdraw from the trial. The total treatment period was approximately 18 months.

Measured Values

	Cetuximab Plus EMD 1201081	Cetuximab Monotherapy
Number of Participants Analyzed	53	53
Progression-free Survival (PFS) Time: Independent Read Assessments [units: months] Median (95% Confidence Interval)	1.5 (1.3 to 2.6)	1.9 (1.5 to 2.9)

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

Statistical Analysis Overview	Comparison Groups	Cetuximab Plus EMD 1201081, Cetuximab Monotherapy
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.793
	Comments	[Not specified]
	Method	Other [Stratified log rank]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	1.1
	Confidence Interval	(2-Sided) 95% 0.7 to 1.6
	Estimation Comments	[Not specified]

2. Secondary Outcome Measure:

Measure Title	Percentage of Participants With Objective Response: Independent Read Assessments
Measure Description	Percentage of participants with objective response based assessment of confirmed complete response (CR) or confirmed partial response (PR) according to Response Evaluation Criteria in Solid Tumors version 1.0 (RECIST v1.0) as assessed by Independent Read. As per RECIST v1.0 for target lesions and assessed by MRI: CR = Disappearance of all target lesions; PR = at least 30% decrease in the sum of the longest diameter of target lesions.
Time Frame	Every 6 weeks until disease progression, reported between day of first participant randomized, that is, 17 Dec 2009 until cut-off date (11 Jan 2012)
Safety Issue?	No

Analysis Population Description

ITT population included all the randomized participants who had received study treatment.

Reporting Groups

	Description
Cetuximab Plus EMD 1201081	Cetuximab weekly (initial dose 400 milligram per square meter [mg/m^2] over 120 minutes followed by 250 mg/m^2 intravenous infusion over 60 minutes) and EMD 1201081 weekly (0.32 milligram per kilogram [mg/kg] by subcutaneous injection) was administered in 3-week treatment cycle until disease progression. Participants who had discontinued cetuximab due to toxicity in cetuximab monotherapy arm, continued to receive EMD 1201081 monotherapy until disease progression or participant elected to withdraw from the trial. The total treatment period was approximately 18 months.
Cetuximab Monotherapy	Cetuximab weekly (initial dose 400 mg/m^2 over 120 minutes followed by 250 mg/m^2 intravenous infusion over 60 minutes) was administered in 3-week treatment cycle until disease progression. Participants who had discontinued cetuximab due to toxicity of cetuximab monotherapy, continued to receive EMD 1201081 monotherapy until disease progression or participant elected to withdraw from the trial. The total treatment period was approximately 18 months.

Measured Values

	Cetuximab Plus EMD 1201081	Cetuximab Monotherapy
Number of Participants Analyzed	53	53
Percentage of Participants With Objective Response: Independent Read Assessments [units: percentage of participants] Number (95% Confidence Interval)	5.7 (1.2 to 15.7)	5.7 (1.2 to 15.7)

Statistical Analysis 1 for Percentage of Participants With Objective Response: Independent Read Assessments

Statistical Analysis Overview	Comparison Groups	Cetuximab Plus EMD 1201081, Cetuximab Monotherapy
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	>0.999
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]

3. Secondary Outcome Measure:

Measure Title	Percentage of Participants With Disease Control: Independent Read Assessments
Measure Description	Percentage of participants with disease control, defined as having achieved CR or PR or stable disease (SD) as the tumor response according to radiological assessments (based on RECIST Version 1.0 criteria), was reported. As per RECIST v1.0 for target lesions and assessed by MRI: CR = disappearance of all target lesions; PR = at least 30% decrease in the sum of the longest diameter of target lesions; SD = neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease.
Time Frame	Every 6 weeks until disease progression, reported between day of first participant randomized, that is, 17 Dec 2009 until cut-off date (11 Jan 2012)
Safety Issue?	No

Analysis Population Description

ITT population included all the randomized participants who had received study treatment.

Reporting Groups

	Description
Cetuximab Plus EMD 1201081	Cetuximab weekly (initial dose 400 milligram per square meter [mg/m^2] over 120 minutes followed by 250 mg/m^2 intravenous infusion over 60 minutes) and EMD 1201081 weekly (0.32 milligram per kilogram [mg/kg] by subcutaneous injection) was administered in 3-week treatment cycle until disease progression. Participants who had discontinued cetuximab due to toxicity in cetuximab monotherapy arm, continued to receive EMD 1201081 monotherapy until disease progression or participant elected to withdraw from the trial. The total treatment period was approximately 18 months.

	Description
Cetuximab Monotherapy	Cetuximab weekly (initial dose 400 mg/m^2 over 120 minutes followed by 250 mg/m^2 intravenous infusion over 60 minutes) was administered in 3-week treatment cycle until disease progression. Participants who had discontinued cetuximab due to toxicity of cetuximab monotherapy, continued to receive EMD 1201081 monotherapy until disease progression or participant elected to withdraw from the trial. The total treatment period was approximately 18 months.

Measured Values

	Cetuximab Plus EMD 1201081	Cetuximab Monotherapy
Number of Participants Analyzed	53	53
Percentage of Participants With Disease Control: Independent Read Assessments [units: percentage of participants] Number (95% Confidence Interval)	37.7 (24.8 to 52.1)	43.4 (29.8 to 57.7)

Statistical Analysis 1 for Percentage of Participants With Disease Control: Independent Read Assessments

Statistical Analysis Overview	Comparison Groups	Cetuximab Plus EMD 1201081, Cetuximab Monotherapy
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.557
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]

4. Secondary Outcome Measure:

Measure Title	Overall Survival (OS) Time
Measure Description	The overall survival (OS) time was defined as the time from randomization to death. Participants without event were censored at the last date known to be alive or at the clinical cut-off date, whatever was earlier.
Time Frame	Time from randomization to death or last day known to be alive, reported between day of first participant randomized, that is, 17 Dec 2009 until cut-off date, (11 Jan 2012)

Safety Issue?	No

Analysis Population Description

ITT population included all the randomized participants who had received study treatment. Overall survival data was analyzed only for participants who received cetuximab plus EMD 1201081.

Reporting Groups

	Description
Cetuximab Plus EMD 1201081	Cetuximab weekly (initial dose 400 milligram per square meter [mg/m^2] over 120 minutes followed by 250 mg/m^2 intravenous infusion over 60 minutes) and EMD 1201081 weekly (0.32 milligram per kilogram [mg/kg] by subcutaneous injection) was administered in 3-week treatment cycle until disease progression. Participants who had discontinued cetuximab due to toxicity in cetuximab monotherapy arm, continued to receive EMD 1201081 monotherapy until disease progression or participant elected to withdraw from the trial. The total treatment period was approximately 18 months.
Cetuximab Monotherapy	Cetuximab weekly (initial dose 400 mg/m^2 over 120 minutes followed by 250 mg/m^2 intravenous infusion over 60 minutes) was administered in 3-week treatment cycle until disease progression. Participants who had discontinued cetuximab due to toxicity of cetuximab monotherapy, continued to receive EMD 1201081 monotherapy until disease progression or participant elected to withdraw from the trial. The total treatment period was approximately 18 months.

Measured Values

	Cetuximab Plus EMD 1201081	Cetuximab Monotherapy
Number of Participants Analyzed	53	0
Overall Survival (OS) Time [units: months] Median (95% Confidence Interval)	6.3 (4.2 to 9.0)	

5. Secondary Outcome Measure:

Measure Title	Number of Participants With Treatment-emergent Adverse Events (TEAEs) and Serious TEAEs
Measure Description	An adverse event (AE) was 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. A Serious AE was an AE that resulted in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial or prolonged inpatient hospitalization; congenital anomaly/birth defect.
Time Frame	Time from first dose up to Day 42 to 49 after last dose of trial treatment, reported between day of first participant randomized, that is, 17 Dec 2009 until cut-off date, (11 Jan 2012)

Safety Issue?	Yes

Analysis Population Description

Safety population included all the participants who received at least 1 dose study drug.

Reporting Groups

	Description
Cetuximab Plus EMD 1201081	Cetuximab weekly (initial dose 400 milligram per square meter [mg/m^2] over 120 minutes followed by 250 mg/m^2 intravenous infusion over 60 minutes) and EMD 1201081 weekly (0.32 milligram per kilogram [mg/kg] by subcutaneous injection) was administered in 3-week treatment cycle until disease progression. Participants who had discontinued cetuximab due to toxicity in cetuximab monotherapy arm, continued to receive EMD 1201081 monotherapy until disease progression or participant elected to withdraw from the trial. The total treatment period was approximately 18 months.
Cetuximab Monotherapy	Cetuximab weekly (initial dose 400 mg/m^2 over 120 minutes followed by 250 mg/m^2 intravenous infusion over 60 minutes) was administered in 3-week treatment cycle until disease progression. Participants who had discontinued cetuximab due to toxicity of cetuximab monotherapy, continued to receive EMD 1201081 monotherapy until disease progression or participant elected to withdraw from the trial. The total treatment period was approximately 18 months.

Measured Values

	Cetuximab Plus EMD 1201081	Cetuximab Monotherapy
Number of Participants Analyzed	54	53
Number of Participants With Treatment-emergent Adverse Events (TEAEs) and Serious TEAEs [units: participants]		
TEAEs	52	53
Serious TEAEs	27	23

Reported Adverse Events

Time Frame	Time from first dose up to Day 42 to 49 after last dose of trial treatment, reported between day of first participant randomized, that is, 17 Dec 2009 until cut-off date, (11 Jan 2012)

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 EMD 1201081	Cetuximab weekly (initial dose 400 milligram per square meter [mg/m^2] over 120 minutes followed by 250 mg/m^2 intravenous infusion over 60 minutes) and EMD 1201081 weekly (0.32 milligram per kilogram [mg/kg] by subcutaneous injection) was administered in 3-week treatment cycle until disease progression. Participants who had discontinued cetuximab due to toxicity in cetuximab monotherapy arm, continued to receive EMD 1201081 monotherapy until disease progression or participant elected to withdraw from the trial. The total treatment period was approximately 18 months.
Cetuximab Monotherapy	Cetuximab weekly (initial dose 400 mg/m^2 over 120 minutes followed by 250 mg/m^2 intravenous infusion over 60 minutes) was administered in 3-week treatment cycle until disease progression. Participants who had discontinued cetuximab due to toxicity of cetuximab monotherapy, continued to receive EMD 1201081 monotherapy until disease progression or participant elected to withdraw from the trial. The total treatment period was approximately 18 months.

Serious Adverse Events

	Cetuximab Plus EMD 1201081	Cetuximab Monotherapy
	Affected/At Risk (%)	Affected/At Risk (%)
Total	27/54 (50%)	23/53 (43.4%)
Cardiac disorders		
CARDIAC FAILURE [A] *	0/54 (0%)	1/53 (1.89%)
PERICARDIAL EFFUSION [A] *	0/54 (0%)	1/53 (1.89%)
Endocrine disorders		
ADDISON'S DISEASE [A] *	0/54 (0%)	1/53 (1.89%)
Gastrointestinal disorders		
ASCITES [A] *	1/54 (1.85%)	0/53 (0%)
DIARRHOEA [A] *	1/54 (1.85%)	0/53 (0%)
DYSPHAGIA [A] *	2/54 (3.7%)	1/53 (1.89%)
ILEUS [A] *	1/54 (1.85%)	0/53 (0%)

	Cetuximab Plus EMD 1201081	Cetuximab Monotherapy
	Affected/At Risk (%)	Affected/At Risk (%)
TONGUE HAEMORRHAGE [A] *	0/54 (0%)	1/53 (1.89%)
General disorders		
DEATH [A] *	0/54 (0%)	1/53 (1.89%)
DEVICE LEAKAGE [A] *	1/54 (1.85%)	0/53 (0%)
DISEASE PROGRESSION [A] *	3/54 (5.56%)	1/53 (1.89%)
FACE OEDEMA [A] *	0/54 (0%)	1/53 (1.89%)
GENERAL PHYSICAL HEALTH DETERIORATION [A] *	1/54 (1.85%)	1/53 (1.89%)
PNEUMATOSIS [A] *	1/54 (1.85%)	0/53 (0%)
PYREXIA [A] *	1/54 (1.85%)	0/53 (0%)
Immune system disorders		
DRUG HYPERSENSITIVITY [A] *	2/54 (3.7%)	0/53 (0%)
Infections and infestations		
BRONCHITIS [A] *	0/54 (0%)	1/53 (1.89%)
BRONCHOPNEUMONIA [A] *	2/54 (3.7%)	0/53 (0%)
CATHETER SITE INFECTION [A] *	2/54 (3.7%)	0/53 (0%)
DEVICE RELATED INFECTION [A] *	1/54 (1.85%)	0/53 (0%)
ERYSIPELAS [A] *	1/54 (1.85%)	0/53 (0%)
PNEUMONIA [A] *	0/54 (0%)	1/53 (1.89%)
PSEUDOMONAL SEPSIS [A] *	0/54 (0%)	1/53 (1.89%)
SUBCUTANEOUS ABSCESS [A] *	1/54 (1.85%)	0/53 (0%)
WOUND INFECTION [A] *	1/54 (1.85%)	0/53 (0%)
Injury, poisoning and procedural complications		

	Cetuximab Plus EMD 1201081	Cetuximab Monotherapy
	Affected/At Risk (%)	Affected/At Risk (%)
GASTROINTESTINAL STOMA COMPLICATION [A] *	1/54 (1.85%)	0/53 (0%)
TRACHEOSTOMY MALFUNCTION [A] *	0/54 (0%)	2/53 (3.77%)
Investigations		
HAEMOGLOBIN DECREASED [A] *	1/54 (1.85%)	0/53 (0%)
Metabolism and nutrition disorders		
CACHEXIA [A] *	1/54 (1.85%)	0/53 (0%)
HYPERCALCAEMIA [A] *	1/54 (1.85%)	0/53 (0%)
HYPERKALAEMIA [A] *	0/54 (0%)	1/53 (1.89%)
MALNUTRITION [A] *	0/54 (0%)	2/53 (3.77%)
Musculoskeletal and connective tissue disorders		
ARTHRITIS [A] *	0/54 (0%)	1/53 (1.89%)
NECK PAIN [A] *	1/54 (1.85%)	0/53 (0%)
PAIN IN EXTREMITY [A] *	1/54 (1.85%)	0/53 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
METASTASES TO LIVER [A] *	0/54 (0%)	1/53 (1.89%)
METASTASES TO MENINGES [A] *	1/54 (1.85%)	0/53 (0%)
TUMOUR HAEMORRHAGE [A] *	0/54 (0%)	2/53 (3.77%)
TUMOUR NECROSIS [A] *	2/54 (3.7%)	0/53 (0%)
Nervous system disorders		
POLYNEUROPATHY [A] *	0/54 (0%)	1/53 (1.89%)
PRESYNCOPE [A] *	1/54 (1.85%)	0/53 (0%)
SPINAL CORD COMPRESSION [A] *	1/54 (1.85%)	0/53 (0%)

	Cetuximab Plus EMD 1201081	Cetuximab Monotherapy
	Affected/At Risk (%)	Affected/At Risk (%)
Psychiatric disorders		
CONFUSIONAL STATE [A] *	0/54 (0%)	1/53 (1.89%)
Renal and urinary disorders		
URETHRAL STENOSIS [A] *	0/54 (0%)	1/53 (1.89%)
Respiratory, thoracic and mediastinal disorders		
DYSPNOEA [A] *	1/54 (1.85%)	3/53 (5.66%)
LARYNGEAL OEDEMA [A] *	1/54 (1.85%)	0/53 (0%)
OBSTRUCTIVE AIRWAYS DISORDER [A] *	1/54 (1.85%)	0/53 (0%)
PNEUMONIA ASPIRATION [A] *	0/54 (0%)	1/53 (1.89%)
PNEUMOTHORAX [A] *	0/54 (0%)	2/53 (3.77%)
RESPIRATORY FAILURE [A] *	3/54 (5.56%)	1/53 (1.89%)
Vascular disorders		
DEEP VEIN THROMBOSIS [A] *	0/54 (0%)	1/53 (1.89%)
HAEMORRHAGE [A] *	1/54 (1.85%)	0/53 (0%)
THROMBOSIS [A] *	0/54 (0%)	1/53 (1.89%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA 14.1

Other Adverse Events

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

	Cetuximab Plus EMD 1201081	Cetuximab Monotherapy
	Affected/At Risk (%)	Affected/At Risk (%)
Total	51/54 (94.44%)	53/53 (100%)
Blood and lymphatic system disorders		
ANAEMIA [A] *	9/54 (16.67%)	5/53 (9.43%)

	Cetuximab Plus EMD 1201081	Cetuximab Monotherapy
	Affected/At Risk (%)	Affected/At Risk (%)
Gastrointestinal disorders		
ABDOMINAL PAIN UPPER [A] *	3/54 (5.56%)	0/53 (0%)
CONSTIPATION [A] *	8/54 (14.81%)	4/53 (7.55%)
DIARRHOEA [A] *	6/54 (11.11%)	10/53 (18.87%)
DYSPHAGIA [A] *	5/54 (9.26%)	5/53 (9.43%)
NAUSEA [A] *	8/54 (14.81%)	4/53 (7.55%)
STOMATITIS [A] *	9/54 (16.67%)	6/53 (11.32%)
VOMITING [A] *	7/54 (12.96%)	3/53 (5.66%)
General disorders		
ASTHENIA [A] *	7/54 (12.96%)	4/53 (7.55%)
CHEST PAIN [A] *	0/54 (0%)	3/53 (5.66%)
CHILLS [A] *	5/54 (9.26%)	1/53 (1.89%)
FATIGUE [A] *	8/54 (14.81%)	12/53 (22.64%)
INJECTION SITE ERYTHEMA [A] *	3/54 (5.56%)	0/53 (0%)
INJECTION SITE INFLAMMATION [A] *	4/54 (7.41%)	0/53 (0%)
INJECTION SITE PAIN [A] *	3/54 (5.56%)	0/53 (0%)
INJECTION SITE REACTION [A] *	11/54 (20.37%)	0/53 (0%)
PYREXIA [A] *	9/54 (16.67%)	3/53 (5.66%)
Infections and infestations		
BRONCHITIS [A] *	2/54 (3.7%)	4/53 (7.55%)
CATHETER SITE INFECTION [A] *	3/54 (5.56%)	0/53 (0%)
NASOPHARYNGITIS [A] *	3/54 (5.56%)	1/53 (1.89%)

	Cetuximab Plus EMD 1201081	Cetuximab Monotherapy
	Affected/At Risk (%)	Affected/At Risk (%)
PNEUMONIA [A] *	1/54 (1.85%)	4/53 (7.55%)
UPPER RESPIRATORY TRACT INFECTION [A] *	3/54 (5.56%)	1/53 (1.89%)
URINARY TRACT INFECTION [A] *	1/54 (1.85%)	5/53 (9.43%)
Metabolism and nutrition disorders		
DECREASED APPETITE [A] *	9/54 (16.67%)	3/53 (5.66%)
DEHYDRATION [A] *	3/54 (5.56%)	4/53 (7.55%)
HYPERCALCAEMIA [A] *	3/54 (5.56%)	4/53 (7.55%)
HYPOKALAEMIA [A] *	4/54 (7.41%)	6/53 (11.32%)
HYPOMAGNESAEMIA [A] *	10/54 (18.52%)	9/53 (16.98%)
HYPONATRAEMIA [A] *	2/54 (3.7%)	3/53 (5.66%)
Musculoskeletal and connective tissue disorders		
ARTHRALGIA [A] *	3/54 (5.56%)	1/53 (1.89%)
BACK PAIN [A] *	3/54 (5.56%)	1/53 (1.89%)
NECK PAIN [A] *	5/54 (9.26%)	3/53 (5.66%)
PAIN IN EXTREMITY [A] *	3/54 (5.56%)	2/53 (3.77%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
CANCER PAIN [A] *	0/54 (0%)	4/53 (7.55%)
INFECTED NEOPLASM [A] *	3/54 (5.56%)	0/53 (0%)
TUMOUR HAEMORRHAGE [A] *	4/54 (7.41%)	1/53 (1.89%)
TUMOUR PAIN [A] *	4/54 (7.41%)	2/53 (3.77%)
Nervous system disorders		
DIZZINESS [A] *	5/54 (9.26%)	2/53 (3.77%)

	Cetuximab Plus EMD 1201081	Cetuximab Monotherapy
	Affected/At Risk (%)	Affected/At Risk (%)
HEADACHE [A] *	5/54 (9.26%)	7/53 (13.21%)
Psychiatric disorders		
ANXIETY [A] *	1/54 (1.85%)	6/53 (11.32%)
INSOMNIA [A] *	4/54 (7.41%)	2/53 (3.77%)
Respiratory, thoracic and mediastinal disorders		
COUGH [A] *	4/54 (7.41%)	3/53 (5.66%)
DYSPNOEA [A] *	7/54 (12.96%)	4/53 (7.55%)
EPISTAXIS [A] *	2/54 (3.7%)	3/53 (5.66%)
PRODUCTIVE COUGH [A] *	4/54 (7.41%)	2/53 (3.77%)
Skin and subcutaneous tissue disorders		
ACNE [A] *	5/54 (9.26%)	4/53 (7.55%)
DERMATITIS ACNEIFORM [A] *	12/54 (22.22%)	16/53 (30.19%)
DRY SKIN [A] *	6/54 (11.11%)	5/53 (9.43%)
ERYTHEMA [A] *	5/54 (9.26%)	0/53 (0%)
HYPERHIDROSIS [A] *	3/54 (5.56%)	0/53 (0%)
PRURITUS [A] *	5/54 (9.26%)	3/53 (5.66%)
RASH [A] *	16/54 (29.63%)	18/53 (33.96%)
SKIN FISSURES [A] *	6/54 (11.11%)	3/53 (5.66%)
Vascular disorders		
HYPERTENSION [A] *	2/54 (3.7%)	3/53 (5.66%)
HYPOTENSION [A] *	3/54 (5.56%)	4/53 (7.55%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA 14.1

Limitations and Caveats

Few of the secondary outcome measures were planned and later removed due to Sponsor's decision to discontinue development of EMD 1201081. Overall survival data was analyzed only for participants who received EMD 1201081 plus cetuximab.

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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