ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: 01/20/2014

ClinicalTrials.gov ID: NCT00463788

Study Identification

Unique Protocol ID:	EMR 200027-051
Brief Title:	Cetuximab and Cisplatin in the Treatment of "Triple Negative" (Estrogen Receptor [ER] Negative, Progesterone Receptor [PgR] Negative, and Human Epidermal Growth Factor Receptor 2 [HER2] Negative) Metastatic Breast Cancer (BALI-1)
Official Title:	Randomized Phase II Trial With Cetuximab and Cisplatin in the Treatment of ER-negative, PgR-negative, HER2-negative Metastatic Breast Carcinoma ("Basal Like")
Secondary IDs:	

Study Status

Record Verification:	January 2014
Overall Status:	Completed
Study Start:	June 2007
Primary Completion:	July 2009 [Actual]
Study Completion:	February 2011 [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: REC reference 2007/02/06 Board Name: SJH/AMNCH Research Ethics Committee Board Affiliation: The Adelaide & Meath Hospital, Dublin Phone: 00353 1 4142860 Email: dan.lynch@amnch.ie
Data Monitoring?:	No
Plan to Share Data?:	
Oversight Authorities:	Australia: Department of Health and Ageing Therapeutic Goods Administration Australia: Human Research Ethics Committee Austria: Ethikkommission Austria: Federal Office for Safety in Health Care Germany: Ethics Commission Germany: Paul-Ehrlich-Institut Ireland: Research Ethics Committee Ireland: Irish Medicines Board Israel: Ethics Commission Italy: National Monitoring Centre for Clinical Trials - Ministry of Health Italy: Ethics Committee New Zealand: Medsafe New Zealand: Ministry of Health Portugal: Ethics Committee for Clinical Research Portugal: National Pharmacy and Medicines Institute Spain: Agencia Española de Medicamentos y Productos Sanitarios Spain: Ethics Committee United Kingdom: Medicines and Healthcare Products Regulatory Agency United Kingdom: Research Ethics Committee

Study Description

Brief Summary:	The primary objective of this study is to determine whether overall response to cetuximab combined with cisplatin is better than overall response to cisplatin alone together with showing that the overall response for cetuximab and cisplatin was above a pre-specified threshold of 0.2 in the treatment of "triple negative" metastatic breast cancer. The secondary objective of this study is to compare the differences between the two treatment groups using the following criteria : Progression-Free Survival (PFS) Time, Overall Survival (OS), Time to Response (TTR) and Safety.
Detailed Description:	

Conditions

Conditions:	Breast Neoplasm
Keywords:	cancer breast metastatic triple negative

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:	Efficacy Study
Enrollment:	181 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: cisplatin and cetuximab	Drug: cetuximab, cisplatin Subjects will receive an initial dose of cetuximab 400 milligram per square meter (mg/m^2) followed by weekly doses of 250 mg/m^2. All doses will be given by intravenous (IV) infusion. Subjects will receive cisplatin (75 mg/m^2 IV on Day 1) every 3 weeks, with a maximum of 6 cycles. Administration of the Investigational Medicinal Product (IMP) will be stopped upon the first occurrence of disease progression, unacceptable toxicity or withdrawal of consent.
Active Comparator: cisplatin	Drug: cisplatin Subjects will receive cisplatin (75 mg/m^2 IV on Day 1) every 3 weeks, with a maximum of 6 cycles. Subjects have the option of receiving cetuximab plus cisplatin at progression within the first 6 cycles, or cetuximab alone at progression after the 6 cycles. Administration of the IMP will be stopped upon the first occurrence of disease progression (except in cisplatin arm where switch to cetuximab plus cisplatin, or

Arms	Assigned Interventions
	cetuximab alone is possible), unacceptable toxicity or withdrawal of consent.

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age:

Gender: Female

Accepts Healthy Volunteers?: No

Criteria: Inclusion Criteria:

- Histologically confirmed diagnosis of metastatic breast cancer (Stage IV)
- Estrogen Receptor [ER] negative, PgR negative and HER2 less than 3+ expression by immunohistochemistry (IHC)
- No more than 1 prior chemotherapy received for treating this metastatic breast cancer
- No more than 1 prior anthracycline and/or taxane regimen (either adjuvant or metastatic setting)
- Other protocol-defined inclusion criteria may apply

Exclusion Criteria:

- Prior platinum agent
- Prior mitomycin
- Known history of brain metastases
- Other protocol-defined exclusion criteria may apply

Contacts/Locations

Study Officials: José Baselga, Prof.
Study Principal Investigator
General Hospital, Boston, Massachusetts, USA

Locations: Austria
Research Site
Salzburg, Austria

Research Site
Wien, Austria

Belgium
Research Site
Brussels, Belgium

Research Site
Wilrijk, Belgium

Research Site
Edegem, Belgium

Germany
Research Site
München, Germany

Research Site
Frankfurt am Main, Germany

Research Site
Kiel, Germany

Research Site
Rostock, Germany

Research Site
Heidelberg, Germany

Ireland
Research Site
Dublin, Ireland

Israel
Research Site
Beer Sheba, Israel

Research Site
Tel Aviv, Israel

Research Site
Petah Tikva, Israel

Research Site
Tel Hashomer, Israel

Research Site
Haifa, Israel

Italy
Research Site
Genova, Italy

Portugal
Research Site
Lisboa, Portugal

Research Site
Porto, Portugal

Spain
Research Site
Barcelona, Spain

Research Site
Valencia, Spain

Research Site
Madrid, Spain

Research Site
Zaragoza, Spain

Research Site
Palma de Mallorca, Spain

Austria
Research Site
Bludesch-Gais, Austria

Israel
Research Site
Rehovot, Israel

United Kingdom
Research Site
London, United Kingdom

Research Site
Manchester, United Kingdom

Germany
Research Site
Köln, Germany

Italy
Research Site
Modena, Italy

United Kingdom
Research Site
Cardiff, United Kingdom

Belgium
Research Site
Liège, Belgium

Research Site
Namur, Belgium

Research Site
Gent, Belgium

Australia, Western Australia
Research Site
Perth, Western Australia, Australia

Australia, New South Wales
Research Site
Wollongong, New South Wales, Australia

Australia, Victoria
Research Site
Malvern, Victoria, Australia

Australia, New South Wales
Research Site
Liverpool, New South Wales, Australia

Research Site
Campbelltown, New South Wales, Australia

Israel
Research Site
Kefar Sava, Israel

Research Site
Jerusalem, Israel

New Zealand
Research Site

Wellington, New Zealand

Research Site
Christchurch, New Zealand

Portugal
Research Site
Coimbra, Portugal

Spain
Research Site
Murcia, Spain

United Kingdom
Research Site
Guildford, United Kingdom

References

Citations:

Links:

Study Data/Documents:

Study Results

Participant Flow

Pre-Assignment Details	Following a mandate of the Spanish health authority, data from all participants at site 0904 (Spain) were excluded from analyses due to evidence of misconduct, with significant deviations from Good Clinical Practice guidelines. Therefore, 173 of the 181 randomized participants were considered in the full analysis set (FAS).

Reporting Groups

	Description
Cisplatin and Cetuximab	Cisplatin 75 milligram per square meter (mg/m^2) intravenous (IV) infusion administered on Day 1 until every 3 weeks with a maximum of 6 cycles and cetuximab initially 400 mg/m^2 followed by 250 mg/m^2 IV infusion weekly. Participants who demonstrated at least stable disease (SD) up to 6 cycles of cisplatin continued treatment with cetuximab only until progressive disease (PD) or occurrence of unacceptable toxicity.

	Description
Cisplatin	Cisplatin 75 mg/m^2 IV infusion administered on Day 1 until every 3 weeks with a maximum of 6 cycles until the first occurrence of PD, unacceptable toxicity or withdrawal of consent.

Overall Study

	Cisplatin and Cetuximab	Cisplatin
Started	115	58
Treated	114	57
Completed	6	4
Not Completed	109	54
Progressive Disease	86	42
Adverse Event	6	2
Withdrawal by Subject	6	2
Death	4	3
Symptomatic Deterioration	2	3
Lost to Follow-up	1	0
Protocol Violation	0	1
Unspecified	3	0
Randomized but not treated	1	1

Baseline Characteristics

Reporting Groups

	Description
Cisplatin and Cetuximab	Cisplatin 75 milligram per square meter (mg/m^2) intravenous (IV) infusion administered on Day 1 until every 3 weeks with a maximum of 6 cycles and cetuximab initially 400 mg/m^2 followed by 250 mg/m^2 IV infusion weekly. Participants who demonstrated at least stable disease (SD) up to 6 cycles of cisplatin continued treatment with cetuximab only until progressive disease (PD) or occurrence of unacceptable toxicity.
Cisplatin	Cisplatin 75 mg/m^2 IV infusion administered on Day 1 until every 3 weeks with a maximum of 6 cycles until the first occurrence of PD, unacceptable toxicity or withdrawal of consent.

Baseline Measures

	Cisplatin and Cetuximab	Cisplatin	Total
Number of Participants	115	58	173
Age, Continuous [units: years] Mean (Standard Deviation)	52.9 (12.53)	51.7 (10.67)	52.5 (11.92)
Age, Customized [units: participants]			
< 65 years	93	51	144
>= 65 years	22	7	29
Gender, Male/Female [units: participants]			
Female	115	58	173
Male	0	0	0
Naturally post menopausal participants [units: participants]			
Yes	64	36	100
No	51	22	73
Duration of breast cancer from primary tumor diagnosis to informed consent [1] [units: months] Median (Full Range)	19.2 (0.0 to 350.0)	17.3 (0.0 to 199.0)	18.7 (0.0 to 350.0)
Participants categorized by site of metastasis [2] [units: participants]			
Lung	64	26	90
Lymph nodes (by medical review)	49	22	71
Bone	37	20	57
Liver	36	17	53
Skin	20	8	28
Other	15	8	23

	Cisplatin and Cetuximab	Cisplatin	Total
Duration of metastatic breast cancer from metastasis to informed consent [3] [units: months] Median (Full Range)	0.9 (0.0 to 56.0)	0.8 (0.0 to 41.0)	0.9 (0.0 to 56.0)
Duration from initial breast cancer diagnosis to date of metastasis [4] [units: months] Median (Full Range)	15.7 (0.0 to 349.0)	15.4 (-4.0 to 199.0)	15.5 (-4.0 to 349.0)

[1] Number of participants analyzed "N" are 110 and 56 for each arm group respectively for this specific parameter.

[2] A participant can have more than one site of metastasis.

[3] Number of participants analyzed "N" are 113 and 56 for each arm group respectively for this specific parameter.

[4] Number of participants analyzed "N" are 108 and 55 for each arm group respectively for this specific parameter.

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Best Overall Response (BOR)
Measure Description	Percentage of participants with best overall (objective) response based assessment of confirmed complete response (CR) or confirmed partial response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST).
Time Frame	Evaluations were performed every 6 weeks until progression reported between day of first participant randomized, 20 June 2007, until cut-off date, 31 July 2009
Safety Issue?	No

Analysis Population Description

FAS population included all participants who were randomized as described in the pre-assignment details.

Reporting Groups

	Description
Cisplatin and Cetuximab	Cisplatin 75 milligram per square meter (mg/m^2) intravenous (IV) infusion administered on Day 1 until every 3 weeks with a maximum of 6 cycles and cetuximab initially 400 mg/m^2 followed by 250 mg/m^2 IV infusion weekly. Participants who demonstrated at least stable disease (SD) up to 6 cycles of cisplatin continued treatment with cetuximab only until progressive disease (PD) or occurrence of unacceptable toxicity.

	Description
Cisplatin	Cisplatin 75 mg/m^2 IV infusion administered on Day 1 until every 3 weeks with a maximum of 6 cycles until the first occurrence of PD, unacceptable toxicity or withdrawal of consent.

Measured Values

	Cisplatin and Cetuximab	Cisplatin
Number of Participants Analyzed	115	58
Best Overall Response (BOR) [units: percentage of participants] Number (95% Confidence Interval)	20.0 (13.1 to 28.5)	10.3 (3.9 to 21.2)

Statistical Analysis 1 for Best Overall Response (BOR)

Statistical Analysis Overview	Comparison Groups	Cisplatin and Cetuximab, Cisplatin
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.1109
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	Randomization strata: first- or second line according to Interactive Voice Response System (IVRS).

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	2.126
	Confidence Interval	(2-Sided) 95% 0.809 to 5.591
	Estimation Comments	[Not specified]

2. Secondary Outcome Measure:

Measure Title	Progression-Free Survival (PFS) Time

Measure Description	The PFS was defined as the duration from randomization until radiological progression according to investigator (based on RECIST) or death due to any cause. Only deaths within 85 days of last tumor assessment were considered. Participants without event were censored on the date of last tumor assessment.
Time Frame	Time from randomization to disease progression, death or last tumour assessment, reported between day of first participant randomized, 20 June 2007, until cut-off date, 31 July 2009
Safety Issue?	No

Analysis Population Description

FAS population included all participants who were randomized as described in the pre-assignment details.

Reporting Groups

	Description
Cisplatin and Cetuximab	Cisplatin 75 milligram per square meter (mg/m^2) intravenous (IV) infusion administered on Day 1 until every 3 weeks with a maximum of 6 cycles and cetuximab initially 400 mg/m^2 followed by 250 mg/m^2 IV infusion weekly. Participants who demonstrated at least stable disease (SD) up to 6 cycles of cisplatin continued treatment with cetuximab only until progressive disease (PD) or occurrence of unacceptable toxicity.
Cisplatin	Cisplatin 75 mg/m^2 IV infusion administered on Day 1 until every 3 weeks with a maximum of 6 cycles until the first occurrence of PD, unacceptable toxicity or withdrawal of consent.

Measured Values

	Cisplatin and Cetuximab	Cisplatin
Number of Participants Analyzed	115	58
Progression-Free Survival (PFS) Time [units: months] Median (95% Confidence Interval)	3.7 (2.8 to 4.3)	1.5 (1.4 to 2.8)

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

Statistical Analysis Overview	Comparison Groups	Cisplatin and Cetuximab, Cisplatin
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0324
	Comments	[Not specified]

	Method	Log Rank
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	0.675
	Confidence Interval	(2-Sided) 95% 0.470 to 0.969
	Estimation Comments	[Not specified]

3. Secondary Outcome Measure:

Measure Title	Overall Survival (OS) Time
Measure Description	The 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, 20 June 2007, until cut-off date, 05 April 2010
Safety Issue?	No

Analysis Population Description

FAS population included all participants who were randomized as described in the pre-assignment details.

Reporting Groups

	Description
Cisplatin and Cetuximab	Cisplatin 75 milligram per square meter (mg/m^2) intravenous (IV) infusion administered on Day 1 until every 3 weeks with a maximum of 6 cycles and cetuximab initially 400 mg/m^2 followed by 250 mg/m^2 IV infusion weekly. Participants who demonstrated at least stable disease (SD) up to 6 cycles of cisplatin continued treatment with cetuximab only until progressive disease (PD) or occurrence of unacceptable toxicity.
Cisplatin	Cisplatin 75 mg/m^2 IV infusion administered on Day 1 until every 3 weeks with a maximum of 6 cycles until the first occurrence of PD, unacceptable toxicity or withdrawal of consent.

Measured Values

	Cisplatin and Cetuximab	Cisplatin
Number of Participants Analyzed	115	58
Overall Survival (OS) Time [units: months] Median (95% Confidence Interval)	12.9 (9.6 to 15.6)	9.4 (6.7 to 14.2)

Statistical Analysis 1 for Overall Survival (OS) Time

Statistical Analysis Overview	Comparison Groups	Cisplatin and Cetuximab, Cisplatin
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.3121
	Comments	[Not specified]
	Method	Log Rank
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	0.821
	Confidence Interval	(2-Sided) 95% 0.561 to 1.204
	Estimation Comments	[Not specified]

4. Secondary Outcome Measure:

Measure Title	Time to Response (TTR)
Measure Description	The TTR was determined for participants whose confirmed BOR (based on RECIST) was either a CR or a PR . It was defined as the time from the first dose study treatment until the date of the first assessment of confirmed CR or PR.
Time Frame	Time from the first dose of study treatment (cetuximab or cisplatin) to first assessment of CR or PR, reported between day of first participant randomized, 20 June 2007, until cut-off date, 31 July 2009
Safety Issue?	No

Analysis Population Description

FAS population included all participants who were randomized as described in the pre-assignment details.

Reporting Groups

	Description
Cisplatin and Cetuximab	Cisplatin 75 milligram per square meter (mg/m^2) intravenous (IV) infusion administered on Day 1 until every 3 weeks with a maximum of 6 cycles and cetuximab initially 400 mg/m^2 followed by 250 mg/m^2 IV infusion weekly. Participants who demonstrated at least stable disease (SD) up to 6 cycles of cisplatin continued treatment with cetuximab only until progressive disease (PD) or occurrence of unacceptable toxicity.
Cisplatin	Cisplatin 75 mg/m^2 IV infusion administered on Day 1 until every 3 weeks with a maximum of 6 cycles until the first occurrence of PD, unacceptable toxicity or withdrawal of consent.

Measured Values

	Cisplatin and Cetuximab	Cisplatin
Number of Participants Analyzed	115	58
Time to Response (TTR) [units: months] Median (95% Confidence Interval)	1.4 (1.3 to 1.4)	1.3 (1.2 to 1.4)

Statistical Analysis 1 for Time to Response (TTR)

Statistical Analysis Overview	Comparison Groups	Cisplatin and Cetuximab, Cisplatin
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.5993
	Comments	[Not specified]
	Method	Log Rank
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	0.754
	Confidence Interval	(2-Sided) 95% 0.262 to 2.170
	Estimation Comments	[Not specified]

5. Secondary Outcome Measure:

Measure Title	Safety- Number of Participants Experiencing Any Adverse Event (AE)
Measure Description	Number of participants experiencing any AE. AEs: Any untoward medical occurrence in the form of signs, clinically significant abnormalities in laboratory findings, diseases, symptoms, or worsening of complications.
Time Frame	Time from first dose up to 30 days after last dose of study treatment, reported between day of first dose of study treatment, 20 June 2007, until cut-off date 05 April 2010
Safety Issue?	Yes

Analysis Population Description

Safety population included all the participants who received at least 1 dose of study medication (that is cisplatin or cetuximab).

Reporting Groups

	Description
Cisplatin and Cetuximab	Cisplatin 75 milligram per square meter (mg/m^2) intravenous (IV) infusion administered on Day 1 until every 3 weeks with a maximum of 6 cycles and cetuximab initially 400 mg/m^2 followed by 250 mg/m^2 IV infusion weekly. Participants who demonstrated at least stable disease (SD) up to 6 cycles of cisplatin continued treatment with cetuximab only until progressive disease (PD) or occurrence of unacceptable toxicity.
Cisplatin	Cisplatin 75 mg/m^2 IV infusion administered on Day 1 until every 3 weeks with a maximum of 6 cycles until the first occurrence of PD, unacceptable toxicity or withdrawal of consent.

Measured Values

	Cisplatin and Cetuximab	Cisplatin
Number of Participants Analyzed	114	57
Safety- Number of Participants Experiencing Any Adverse Event (AE) [units: participants]	114	57

Reported Adverse Events

Time Frame	Time from first dose up to 30 days after last dose of study treatment, reported between day of first dose of study treatment, 20 June 2007, until cut-off date 05 April 2010

Additional Description	An 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 IMP, regardless of causal relationship.

Reporting Groups

	Description
Cisplatin and Cetuximab	Cisplatin 75 milligram per square meter (mg/m^2) intravenous (IV) infusion administered on Day 1 until every 3 weeks with a maximum of 6 cycles and cetuximab initially 400 mg/m^2 followed by 250 mg/m^2 IV infusion weekly.
Cisplatin	Cisplatin 75 mg/m^2 IV infusion administered on Day 1 until every 3 weeks with a maximum of 6 cycles until the first occurrence of progressive disease (PD), unacceptable toxicity or withdrawal of consent.
Cisplatin Alone Switched to Cetuximab	On progression, participants in the cisplatin group had the option to switch to cisplatin (75 mg/m^2 IV infusion) plus cetuximab (initially 400 mg/m^2 followed by 250 mg/m^2 IV infusion) if the progressive disease was reported during the 6 cisplatin cycles or to cetuximab alone (initially 400 mg/m^2 followed by 250 mg/m^2 IV infusion) if the progression was reported after the 6 cisplatin cycles.

Serious Adverse Events

	Cisplatin and Cetuximab	Cisplatin	Cisplatin Alone Switched to Cetuximab
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	41/114 (35.96%)	13/57 (22.81%)	6/31 (19.35%)
Blood and lymphatic system disorders			
Anaemia [A] *	3/114 (2.63%)	0/57 (0%)	0/31 (0%)
Leukopenia [A] *	1/114 (0.88%)	0/57 (0%)	0/31 (0%)
Thrombocytopenia [A] *	1/114 (0.88%)	0/57 (0%)	0/31 (0%)
Cardiac disorders			
Tachycardia [A] *	0/114 (0%)	1/57 (1.75%)	0/31 (0%)
Gastrointestinal disorders			
Abdomial Pain [A] *	1/114 (0.88%)	0/57 (0%)	0/31 (0%)
Abdominal Distention [A] *	1/114 (0.88%)	0/57 (0%)	0/31 (0%)
Diarrhoea [A] *	3/114 (2.63%)	0/57 (0%)	0/31 (0%)
Intestinal Obstruction [A] *	0/114 (0%)	1/57 (1.75%)	0/31 (0%)

	Cisplatin and Cetuximab	Cisplatin	Cisplatin Alone Switched to Cetuximab
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Melaena [A] *	1/114 (0.88%)	0/57 (0%)	0/31 (0%)
Nausea [A] *	2/114 (1.75%)	0/57 (0%)	0/31 (0%)
Vomiting [A] *	1/114 (0.88%)	1/57 (1.75%)	0/31 (0%)
General disorders			
Asthenia [A] *	2/114 (1.75%)	0/57 (0%)	0/31 (0%)
Fatigue [A] *	3/114 (2.63%)	0/57 (0%)	0/31 (0%)
General Physical Health Deterioration [A] *	4/114 (3.51%)	1/57 (1.75%)	2/31 (6.45%)
Pyrexia [A] *	4/114 (3.51%)	2/57 (3.51%)	1/31 (3.23%)
Hepatobiliary disorders			
Hepatic Function Abnormal [A] *	1/114 (0.88%)	0/57 (0%)	0/31 (0%)
Immune system disorders			
Drug Hypersensitivity [A] *	1/114 (0.88%)	0/57 (0%)	0/31 (0%)
Infections and infestations			
Catheter Site Infection [A] *	1/114 (0.88%)	0/57 (0%)	0/31 (0%)
Cellulitis [A] *	1/114 (0.88%)	0/57 (0%)	0/31 (0%)
Device Related Infection [A] *	1/114 (0.88%)	0/57 (0%)	0/31 (0%)
Erysipelas [A] *	1/114 (0.88%)	0/57 (0%)	0/31 (0%)
Infection [A] *	1/114 (0.88%)	0/57 (0%)	0/31 (0%)
Pneumonia [A] *	2/114 (1.75%)	1/57 (1.75%)	0/31 (0%)
Post Procedural Infection [A] *	0/114 (0%)	1/57 (1.75%)	0/31 (0%)
Septic Shock [A] *	1/114 (0.88%)	0/57 (0%)	1/31 (3.23%)
Sinusitis [A] *	0/114 (0%)	1/57 (1.75%)	0/31 (0%)

	Cisplatin and Cetuximab	Cisplatin	Cisplatin Alone Switched to Cetuximab
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Skin Infection [A] *	0/114 (0%)	1/57 (1.75%)	0/31 (0%)
Soft Tissue Infection [A] *	1/114 (0.88%)	0/57 (0%)	0/31 (0%)
Streptococcal Infection [A] *	1/114 (0.88%)	0/57 (0%)	0/31 (0%)
Urinary Tract Infection [A] *	1/114 (0.88%)	0/57 (0%)	0/31 (0%)
Injury, poisoning and procedural complications			
Femur Fracture [A] *	0/114 (0%)	0/57 (0%)	1/31 (3.23%)
Investigations			
Oxygen Saturation Decreased [A] *	1/114 (0.88%)	0/57 (0%)	0/31 (0%)
Metabolism and nutrition disorders			
Decreased Appetite [A] *	1/114 (0.88%)	0/57 (0%)	0/31 (0%)
Hypocalcaemia [A] *	1/114 (0.88%)	0/57 (0%)	0/31 (0%)
Hypomagnesaemia [A] *	1/114 (0.88%)	0/57 (0%)	0/31 (0%)
Hyponatraemia [A] *	1/114 (0.88%)	0/57 (0%)	0/31 (0%)
Musculoskeletal and connective tissue disorders			
Back Pain [A] *	1/114 (0.88%)	0/57 (0%)	0/31 (0%)
Osteolysis [A] *	1/114 (0.88%)	0/57 (0%)	0/31 (0%)
Pathological Fracture [A] *	0/114 (0%)	1/57 (1.75%)	0/31 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer Pain [A] *	0/114 (0%)	0/57 (0%)	1/31 (3.23%)
Metastases to Central Nervous System [A] *	1/114 (0.88%)	1/57 (1.75%)	0/31 (0%)
Nervous system disorders			
Cerebral Haemorrhage [A] *	1/114 (0.88%)	0/57 (0%)	0/31 (0%)

	Cisplatin and Cetuximab	Cisplatin	Cisplatin Alone Switched to Cetuximab
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Cerebrovascular Accident [A] *	0/114 (0%)	1/57 (1.75%)	0/31 (0%)
Coma Hepatic [A] *	1/114 (0.88%)	0/57 (0%)	0/31 (0%)
Dizziness [A] *	1/114 (0.88%)	0/57 (0%)	0/31 (0%)
Headache [A] *	2/114 (1.75%)	0/57 (0%)	0/31 (0%)
Renal and urinary disorders			
Renal Failure [A] *	1/114 (0.88%)	0/57 (0%)	0/31 (0%)
Reproductive system and breast disorders			
Pelvic Pain [A] *	1/114 (0.88%)	0/57 (0%)	0/31 (0%)
Respiratory, thoracic and mediastinal disorders			
Cough [A] *	2/114 (1.75%)	0/57 (0%)	0/31 (0%)
Dysphonia [A] *	1/114 (0.88%)	0/57 (0%)	0/31 (0%)
Dyspnoae [A] *	6/114 (5.26%)	1/57 (1.75%)	0/31 (0%)
Pleural Effusion [A] *	2/114 (1.75%)	1/57 (1.75%)	0/31 (0%)
Pneumothorax [A] *	1/114 (0.88%)	0/57 (0%)	0/31 (0%)
Pulmonary Embolism [A] *	4/114 (3.51%)	0/57 (0%)	2/31 (6.45%)
Respiratory Failure [A] *	1/114 (0.88%)	0/57 (0%)	0/31 (0%)
Vascular disorders			
Arterial Thrombosis Limb [A] *	1/114 (0.88%)	0/57 (0%)	0/31 (0%)
Deep Vein Thrombosis [A] *	1/114 (0.88%)	0/57 (0%)	0/31 (0%)
Hypertension [A] *	1/114 (0.88%)	0/57 (0%)	0/31 (0%)
Thrombosis [A] *	0/114 (0%)	1/57 (1.75%)	0/31 (0%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA (10.0)

Other Adverse Events

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

	Cisplatin and Cetuximab	Cisplatin	Cisplatin Alone Switched to Cetuximab
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	112/114 (98.25%)	55/57 (96.49%)	28/31 (90.32%)
Blood and lymphatic system disorders			
Anaemia [A] *	13/114 (11.4%)	12/57 (21.05%)	4/31 (12.9%)
Leukopenia [A] *	7/114 (6.14%)	1/57 (1.75%)	0/31 (0%)
Neutropenia [A] *	33/114 (28.95%)	10/57 (17.54%)	3/31 (9.68%)
Thrombocytopenia [A] *	7/114 (6.14%)	2/57 (3.51%)	0/31 (0%)
Ear and labyrinth disorders			
Ototoxicity [A] *	3/114 (2.63%)	3/57 (5.26%)	0/31 (0%)
Tinnitus [A] *	8/114 (7.02%)	10/57 (17.54%)	0/31 (0%)
Vertigo [A] *	1/114 (0.88%)	3/57 (5.26%)	0/31 (0%)
Eye disorders			
Conjunctivitis [A] *	9/114 (7.89%)	0/57 (0%)	0/31 (0%)
Gastrointestinal disorders			
Abdominal Pain [A] *	10/114 (8.77%)	1/57 (1.75%)	2/31 (6.45%)
Abdominal Pain Upper [A] *	9/114 (7.89%)	6/57 (10.53%)	0/31 (0%)
Constipation [A] *	27/114 (23.68%)	16/57 (28.07%)	5/31 (16.13%)
Diarrhoea [A] *	22/114 (19.3%)	6/57 (10.53%)	3/31 (9.68%)
Dyspepsia [A] *	13/114 (11.4%)	5/57 (8.77%)	0/31 (0%)
Nausea [A] *	73/114 (64.04%)	37/57 (64.91%)	8/31 (25.81%)
Stomatitis [A] *	16/114 (14.04%)	2/57 (3.51%)	2/31 (6.45%)

	Cisplatin and Cetuximab	Cisplatin	Cisplatin Alone Switched to Cetuximab
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Vomiting [A] *	43/114 (37.72%)	37/57 (64.91%)	7/31 (22.58%)
General disorders			
Asthenia [A] *	26/114 (22.81%)	14/57 (24.56%)	3/31 (9.68%)
Fatigue [A] *	56/114 (49.12%)	20/57 (35.09%)	6/31 (19.35%)
General Physical Health Deterioration [A] *	4/114 (3.51%)	4/57 (7.02%)	0/31 (0%)
Mucosal Inflammation [A] *	0/114 (0%)	0/57 (0%)	2/31 (6.45%)
Oedema Peripheral [A] *	10/114 (8.77%)	3/57 (5.26%)	0/31 (0%)
Pain [A] *	9/114 (7.89%)	1/57 (1.75%)	2/31 (6.45%)
Pyrexia [A] *	11/114 (9.65%)	7/57 (12.28%)	0/31 (0%)
Immune system disorders			
Drug Hypersensitivity [A] *	6/114 (5.26%)	0/57 (0%)	0/31 (0%)
Infections and infestations			
Folliculitis [A] *	0/114 (0%)	0/57 (0%)	2/31 (6.45%)
Nail Infection [A] *	6/114 (5.26%)	0/57 (0%)	0/31 (0%)
Nasopharyngitis [A] *	7/114 (6.14%)	2/57 (3.51%)	0/31 (0%)
Investigations			
Haemoglobin Decreased [A] *	2/114 (1.75%)	3/57 (5.26%)	0/31 (0%)
Weight Decreased [A] *	0/114 (0%)	0/57 (0%)	2/31 (6.45%)
Metabolism and nutrition disorders			
Decreased Appetite [A] *	40/114 (35.09%)	8/57 (14.04%)	4/31 (12.9%)
Hypocalcaemia [A] *	6/114 (5.26%)	0/57 (0%)	2/31 (6.45%)
Hypokalaemia [A] *	15/114 (13.16%)	1/57 (1.75%)	3/31 (9.68%)

	Cisplatin and Cetuximab	Cisplatin	Cisplatin Alone Switched to Cetuximab
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Hypomagnesaemia [A] *	23/114 (20.18%)	4/57 (7.02%)	3/31 (9.68%)
Musculoskeletal and connective tissue disorders			
Back Pain [A] *	8/114 (7.02%)	6/57 (10.53%)	3/31 (9.68%)
Bone Pain [A] *	8/114 (7.02%)	3/57 (5.26%)	0/31 (0%)
Musculoskeletal Pain [A] *	2/114 (1.75%)	4/57 (7.02%)	0/31 (0%)
Pain in Extremity [A] *	13/114 (11.4%)	3/57 (5.26%)	2/31 (6.45%)
Nervous system disorders			
Dysgeusia [A] *	19/114 (16.67%)	4/57 (7.02%)	0/31 (0%)
Headache [A] *	11/114 (9.65%)	7/57 (12.28%)	2/31 (6.45%)
Neuropathy Peripheral [A] *	12/114 (10.53%)	4/57 (7.02%)	0/31 (0%)
Paraesthesia [A] *	4/114 (3.51%)	3/57 (5.26%)	0/31 (0%)
Peripheral Sensory Neuropathy [A] *	13/114 (11.4%)	2/57 (3.51%)	0/31 (0%)
Psychiatric disorders			
Anxiety [A] *	5/114 (4.39%)	3/57 (5.26%)	0/31 (0%)
Depression [A] *	7/114 (6.14%)	2/57 (3.51%)	0/31 (0%)
Insomnia [A] *	5/114 (4.39%)	4/57 (7.02%)	2/31 (6.45%)
Reproductive system and breast disorders			
Breast Pain [A] *	6/114 (5.26%)	0/57 (0%)	0/31 (0%)
Respiratory, thoracic and mediastinal disorders			
Cough [A] *	16/114 (14.04%)	7/57 (12.28%)	4/31 (12.9%)
Dyspnoea [A] *	23/114 (20.18%)	8/57 (14.04%)	3/31 (9.68%)
Skin and subcutaneous tissue disorders			

	Cisplatin and Cetuximab	Cisplatin	Cisplatin Alone Switched to Cetuximab
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Acne [A] *	15/114 (13.16%)	0/57 (0%)	4/31 (12.9%)
Alopecia [A] *	15/114 (13.16%)	3/57 (5.26%)	2/31 (6.45%)
Dermatitis Acneiform [A] *	23/114 (20.18%)	0/57 (0%)	9/31 (29.03%)
Dry Skin [A] *	29/114 (25.44%)	1/57 (1.75%)	2/31 (6.45%)
Nail Disorder [A] *	6/114 (5.26%)	0/57 (0%)	2/31 (6.45%)
Pruritus [A] *	10/114 (8.77%)	2/57 (3.51%)	3/31 (9.68%)
Rash [A] *	56/114 (49.12%)	1/57 (1.75%)	5/31 (16.13%)
Vascular disorders			
Hypertension [A] *	10/114 (8.77%)	2/57 (3.51%)	2/31 (6.45%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA (10.0)

Limitations and Caveats

Participants were randomized to 2 groups in a 2:1 ratio.

More Information

Certain Agreements:

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

There is NOT an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

Results Point of Contact:

Name/Official Title: Merck KGaA Communication Center
Organization: Merck KGaA
Phone: +49-6151-72-5200

Email: service@merckgroup.com