Clinical trial results:
Phase II Clinical Study of Cetuximab in Refractory Colorectal Cancer With K-RAS Mutated and Favourable FcR IIa (CD32) Genotype

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2010-023580-18
Trial protocol	ES
Global end of trial date	10 December 2014

Results information

Result version number	v1 (current)
This version publication date	28 July 2016
First version publication date	28 July 2016

Trial information

Trial identification

Sponsor protocol code	EMR 062202-529

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01450319
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck KGaA
Sponsor organisation address	Frankfurter Strasse 250, Darmstadt, Germany, 64293
Public contact	Communication Centre Merck KGaA, Merck KGaA, +49 6151725200, service@merckgroup.com
Scientific contact	Communication Centre Merck KGaA, Merck KGaA, +49 6151725200, service@merckgroup.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 December 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 December 2014
Global end of trial reached?	Yes
Global end of trial date	10 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This national, multicenter, open-label phase 2 study without any control arm aims to evaluate the activity of cetuximab monotherapy in the treatment of refractory colorectal cancer in subjects with K-RAS mutated and FcγRIIa polymorphism tumors, in which there is no therapeutic alternative for treatment. Failure of the first and second line conventional therapeutic lines was documented.

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 December 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 70
Worldwide total number of subjects	70
EEA total number of subjects	70

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	36

From 65 to 84 years	34
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 73 patients were enrolled in the screening for the trial. Three patients were excluded from the modified intent-to-treat (MITT) because they did not receive any dose of the study drug.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Cetuximab

Arm description:

Cetuximab was administered intravenously every 2 weeks until disease progression, death, or consent withdrawal.

Arm type	Experimental
Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	Erbitux
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cetuximab was administered at a dose of 500 milligram per square meter (mg/m^2) every 2 weeks until disease progression, death, or consent withdrawal.

Number of subjects in period 1	Cetuximab
Started	70
Completed	70

Baseline characteristics

Reporting groups	
Reporting group title	Cetuximab
Reporting group description:	
Cetuximab was administered intravenously every 2 weeks until disease progression, death, or consent withdrawal.	

Reporting group values	Cetuximab	Total	
Number of subjects	70	70	
Age categorical			
Units: Subjects			
Age Continuous			
Units: Years			
arithmetic mean	63.61		
standard deviation	± 10.54	-	
Gender, Male/Female			
Units: Subjects			
Female	34	34	
Male	36	36	

End points

End points reporting groups

Reporting group title	Cetuximab

Reporting group description:

Cetuximab was administered intravenously every 2 weeks until disease progression, death, or consent withdrawal.

Primary: Overall Survival (OS) time

End point title	Overall Survival (OS) time[1]

End point description:

Overall survival was defined as the time from date of informed consent signature until death. Modified intent-to-treat (MITT) analysis set included all the subjects who received study drug treatment.

End point type	Primary

End point timeframe:

From the date of informed consent signature until death, assessed up to 3 years

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The one-sided null hypothesis H0: Median ≤ 5 months was pre-specified and was to be tested at a significance level of 0.025. H0 was rejected, because the lower boundary of the 95%CI of the median OS was 5.42 and thus the median OS presented is statistically significant greater than 5 months.

End point values	Cetuximab			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: Months				
median (confidence interval 95%)	6.71 (5.42 to 8.05)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with Disease control rate (DCR)

End point title	Percentage of subjects with Disease control rate (DCR)

End point description:

DCR was defined as those subjects achieving complete response (CR), partial response (PR) or stable disease (SD), according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v.1.1). For target lesions (TLs), CR was defined as disappearance of all TLs; PR was defined as at least a 30 percent (%) decrease in sum of longest diameter (SLD) of TLs, taking as a reference the baseline (BL) SLD; Stable disease (SD) was defined as neither sufficient decrease in SLD to qualify for PR nor sufficient increase in SLD to qualify for PD; and PD was defined as at least a 20% increase in the SLD of TLs, taking as reference smallest SLD recorded since the treatment started. For non-target lesions (NTLs), CR was defined as the disappearance of all NTLs and normalization of tumor marker levels; SD was defined as persistence of 1 or more NTLs and/or maintenance of tumor marker levels above normal limits. MITT analysis set included all the subjects who received study drug treatment.

End point type	Secondary

End point timeframe:

From the date of informed consent signature until progressive disease, assessed up to 3 years

End point values	Cetuximab			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: Percentage of subjects				
number (not applicable)	22.86			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) time

End point title	Progression Free Survival (PFS) time

End point description:

PFS was defined as the time from informed consent signature until progressive disease (PD) or death, whatever occurred first. Subjects who did not have disease progression or were lost to follow-up, were censored at the date of last contact, known to be alive and progression free; moreover, those subjects who started a new treatment (different from cetuximab), were censored at the date of starting the new treatment. For TLs, PD was defined at least a 20% increase in the SLD, taking as reference the smallest SLD recorded from BL or the appearance of one or more new lesions. For NTLs, PD was defined as the appearance of 1 or more new lesions and/or unequivocal progression of existing NTLs. Subjects without second-line PD or death were censored at the date of last tumor assessment where non-progression was documented. MITT analysis set included all the subjects who received study drug treatment.

End point type	Secondary

End point timeframe:

From the date of informed consent signature until progressive disease (PD) or death, assessed up to 3 years

End point values	Cetuximab			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: Months				
median (confidence interval 95%)	2.53 (2.43 to 2.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Adverse Events (AEs), serious adverse events (SAEs), AEs leading to discontinuation, AEs leading to death

End point title	Number of subjects with Adverse Events (AEs), serious adverse events (SAEs), AEs leading to discontinuation, AEs leading to death

End point description:

An AE was defined as any new untoward medical occurrences/worsening of pre-existing medical condition without regard to possibility of causal relationship. An SAE 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. Treatment-emergent are events between first dose of study drug and up to 30 days after last dose that were absent before treatment or that worsened relative to pretreatment state. Safety analysis set included all the subjects who received at least one dose of the study drug treatment.

End point type	Secondary

End point timeframe:

From the date of enrollment up to 30 days after the last dose of study drug administration, assessed up to 3 years

End point values	Cetuximab			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: subjects				
AEs	69			
SAEs	17			
AEs leading to discontinuation	2			
AEs leading to death	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Fcγ receptors (FCγR) IIa/IIIa polymorphisms

End point title	Number of subjects with Fcγ receptors (FCγR) IIa/IIIa polymorphisms

End point description:

The antibody fragment C portion (FCγ) of cetuximab interacts with Fc-gamma receptors (FCγRs) expressed by immune effector cells. Polymorphisms were described in genes coding for FCγRIIa and in FCγRIIIa. A histidine/arginine polymorphism at position 131 for FCγRIIa gene and valine / phenylalanine polymorphism at position 158 for the FCγRIIIa gene were reported to be functionally relevant in the ADCC mechanism. All subjects were analyzed and classified as carriers of every different polymorphism of FCγ Receptors: for FCγRIIa (H/H, homozygous alleles with histidine and R/H, heterozygous alleles with arginine/histidine) and FCγRIIIa (V/V, homozygous alleles with valine, F/F, homozygous alleles with phenylalanine and F/V, heterozygous alleles with valine / phenylalanine) (units: subjects with every type of polymorphism) .The FCγR genotype was determined using a TaqMan Allelic Discrimination Assay. MITT analysis set included all the subjects who received study drug treatment.

End point type	Secondary

End point timeframe:

Baseline

End point values	Cetuximab			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: subjects				
FcγRIIa: H/H	27			
FcγRIIa: R/H	43			
FcγRIIIa: V/V	6			
FcγRIIIa: F/F	28			
FcγRIIIa: F/V	36			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) Related to Codon G13D

End point title	Overall Survival (OS) Related to Codon G13D

End point description:

OS was defined as the time from informed consent signature until death. Subjects without death were censored at the last date known alive (within the study). MITT analysis set included all the subjects who received study drug treatment. Number of subjects analysed signifies number of evaluable subjects for this endpoint. "n" signifies number of evaluable subjects for each category, as specified. Here "99999" for Confidence interval signifies data not valuated due to lack of events.

End point type	Secondary

End point timeframe:

From the date of informed consent signature until death, lost-to-follow-up or end of study, whatever occurred first (maximal up to 3 years)

End point values	Cetuximab			
Subject group type	Reporting group			
Number of subjects analysed	62			
Units: Months				
median (confidence interval 95%)				
G13D (n=14)	7.2 (4.8 to 99999)			
No G13D (n=48)	6.3 (4.8 to 7.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS) related to Killer Inhibitory Receptors 2DS4 (KIR2DS4) functional receptor (f/d) and non-functional receptor (NFR)

End point title	Overall survival (OS) related to Killer Inhibitory Receptors 2DS4 (KIR2DS4) functional receptor (f/d) and non-functional receptor (NFR)

End point description:

OS was defined as the time from informed consent signature until death. Subjects without death were censored at the last date known alive (within the study). MITT analysis set included all the subjects who received study drug treatment. Number of subjects analysed signifies number of evaluable subjects for this endpoint.

End point type	Secondary

End point timeframe:

From the date of informed consent signature until death, lost-to-follow-up or end of study, whatever occurred first (maximal assessed up to 3 years)

End point values	Cetuximab			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: Months				
median (confidence interval 95%)				
f/d (n=10) NFR (n=56)	4.77 (2.2 to 7.3) 7.4 (6 to 8.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Beta 2-microglobulin

End point title	Beta 2-microglobulin

End point description:

MITT analysis set included all the subjects who received study drug treatment. Number of subjects analysed signifies number of evaluable subjects for this endpoint. "n" signifies number of evaluable subjects for each category, as specified.

End point type	Secondary

End point timeframe:

Baseline, Week 8

End point values	Cetuximab			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: microgram per milliliter (mcg/mL)				
arithmetic mean (standard deviation)				
Baseline (n=61) Week 8 (n=29)	2.35 (± 0.58) 2.37 (± 1.13)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs with onset from the date of enrollment up to 30 days after the last dose of study drug administration; assessed up to 3 years.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Cetuximab

Reporting group description:

Cetuximab was administered intravenously at a dose of 500 milligram per square meter (mg/m^2) every 2 weeks until disease progression, death, or consent withdrawal.

Serious adverse events	Cetuximab		
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 70 (24.29%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events	3		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Disease progression			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	1 / 1		
Cardiac disorders			
Heart failure			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	1 / 70 (1.43%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	1 / 70 (1.43%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General malaise				
subjects affected / exposed	1 / 70 (1.43%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Spontaneous hematoma				
subjects affected / exposed	1 / 70 (1.43%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Bowel obstruction				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 70 (1.43%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholestaticjaundice				
subjects affected / exposed	1 / 70 (1.43%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Acute cholecystitis				
subjects affected / exposed	1 / 70 (1.43%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholangitis				

subjects affected / exposed	1 / 70 (1.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	1 / 1		
Liver failure			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute renal failure			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Pathologic fracture			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Catheter point infection			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			

subjects affected / exposed	1 / 70 (1.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anal abscess			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Listeria meningitis			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	1 / 1		
Metabolism and nutrition disorders			
Hypocalcemia			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Cetuximab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	69 / 70 (98.57%)		
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	10 / 70 (14.29%)		
occurrences (all)	10		
Asthenia			
subjects affected / exposed	32 / 70 (45.71%)		
occurrences (all)	32		
Pyrexia			
subjects affected / exposed	10 / 70 (14.29%)		
occurrences (all)	10		
Oedema peripheral			

subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all)	6 / 70 (8.57%) 6 5 / 70 (7.14%) 5		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	 9 / 70 (12.86%) 9		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Dry mouth subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	 15 / 70 (21.43%) 15 12 / 70 (17.14%) 12 11 / 70 (15.71%) 11 8 / 70 (11.43%) 8 9 / 70 (12.86%) 9 7 / 70 (10.00%) 7 6 / 70 (8.57%) 6		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) Cough	 8 / 70 (11.43%) 8 		

subjects affected / exposed	7 / 70 (10.00%)		
occurrences (all)	7		
Epistaxis			
subjects affected / exposed	4 / 70 (5.71%)		
occurrences (all)	4		
Catarrh			
subjects affected / exposed	4 / 70 (5.71%)		
occurrences (all)	4		
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	4 / 70 (5.71%)		
occurrences (all)	4		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	39 / 70 (55.71%)		
occurrences (all)	39		
Skin toxicity			
subjects affected / exposed	8 / 70 (11.43%)		
occurrences (all)	8		
Pruritus			
subjects affected / exposed	8 / 70 (11.43%)		
occurrences (all)	8		
Skin fissures			
subjects affected / exposed	8 / 70 (11.43%)		
occurrences (all)	8		
Dermatitis			
subjects affected / exposed	8 / 70 (11.43%)		
occurrences (all)	8		
Acne			
subjects affected / exposed	7 / 70 (10.00%)		
occurrences (all)	7		
Dry skin			
subjects affected / exposed	6 / 70 (8.57%)		
occurrences (all)	6		
Psychiatric disorders			

Insomnia subjects affected / exposed occurrences (all)	5 / 70 (7.14%) 5		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all)	 10 / 70 (14.29%) 10 5 / 70 (7.14%) 5		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hypomagnesaemia subjects affected / exposed occurrences (all)	 16 / 70 (22.86%) 16 9 / 70 (12.86%) 9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 March 2011	The main protocol change was the modification of inclusion criteria to add a reference to the following treatments: 5-Fluorouracil (5-FU), Capecitabine, Irinotecan, Oxaliplatin or Bevacizumab.
10 April 2012	- The primary objective was changed to OS. - Some secondary objectives were changed (time to progression [TTP] analysis to objective response rate [ORR] analysis) and new ones (molecular analyses) were added. - Treatment administration length was changed (from 60 minutes in previous version, to the following schedule: 120 minutes in first cycle followed by 90 minutes for second cycle and 60 minutes for third cycle onwards). - The inclusion criteria were changed: to eliminate the age upper limit, to include the heterozygous and/or homozygous genotypes in FcγRIIa. However, FcγRIIIa was not included due to the low frequency of the polymorphism, to change the previous cancer treatment requirements (only two chemotherapy lines). - The sample size was increased, from 55 in previous version, to 70 patients.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported