Clinical trial results:
In vivo response monitoring of treatment with the EGFR-monoclonal-antibody Cetuximab in metastatic colorectal cancer – a single center phase II study

Summary

EudraCT number	2009-013279-23
Trial protocol	DE
Global end of trial date	21 December 2016

Results information

Result version number	v1 (current)
This version publication date	
First version publication date	
Summary attachment (see zip file)	Summary Error Message EudraCT 20220321 (Summary Error Message EudraCT 20220321.pdf)

Trial information

Trial identification

Sponsor protocol code	NCT-2008-11-02-1020

Additional study identifiers

ISRCTN number	ISRCTN75334801
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ruprecht-Karls-University Heidelberg, Medical Faculty
Sponsor organisation address	Im Neuenheimer Feld 672, Heidelberg, Germany, 69120
Public contact	Project Manager, University Hospital Heidelberg, National Centre for Tumor Diseases Heidelberg, 49 6221566296, jennifer.ose@med.uni-heidelberg.de
Scientific contact	Coordinating Investigator, University Hospital Heidelberg, National Centre for Tumor Diseases Heidelberg, 49 6221564801, anne.berger@med.uni-heidelberg.de

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	24 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 December 2016
Global end of trial reached?	Yes
Global end of trial date	21 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the prognostic relevance of relative changes in SUV (as measured in 18F-FDG PET-CT at day 14 versus baseline) for early clinical response (as defined by RECIST, measured at day 56) during short-term single agent treatment with the EGFR-mAB cetuximab

Protection of trial subjects:

- regular DMC meetings
- adherence to all ethical and legal recruitment

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 September 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

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)	25
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

- Histologically confirmed metastatic colorectal cancer / RAS-wildtype
- No history of therapy with an EGFR targeting agent
- No history of previous chemotherapy for advanced disease
- Measurable tumor lesion, diameter no smaller than 1.0 cm detected by CT/MRI/ultrasound
- Life expectancy > 12 weeks

Period 1

Period 1 title	single-arm study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Single Arm: Treatment with Cetuximab

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Cetuximab
Investigational medicinal product code	IMC-C225
Other name	Erbitux
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cetuximab will be administered i.v. 400 mg/m2 bsa on day 1 and 250 mg/m2 bsa on day 8. The solution should be clear and colorless. The infusion will be administered over 120 minutes for the first time and for the following infusions over 60 minutes if no infusion reactions appear. Prior to the first infusion, patients must receive premedication with an antihistamine and a corticosteroid(≥8mg dexamethasone or equivalent). This premedication is recommended prior to all subsequent infusions. The duration of treatment will be two weeks. After day 14, chemotherapy will be routinely applied according to the Folfiri-cetuximab regimen until d56. Depending on the clinical response on day 56, treatment will be continued according to the choice of the responsible physician. It is recommended that, in case of response, t

Number of subjects in period 1	Single Arm: Treatment with Cetuximab
Started	40
Completed	36
Not completed	4
Adverse event, non-fatal	3
Consent withdrawn by subject	1

Baseline characteristics

Reporting groups	
Reporting group title	single-arm study

Reporting group description: -

Reporting group values	single-arm study	Total	
Number of subjects	40	40	
Age categorical			
Birthyear is documented. Day and month are set to July 1st to get the birthdate. Age is calculated as floor of screening date minus birthdate.			
Units: Subjects			
From 18 to 44	1	1	
From 45 to 65	24	24	
>=65	15	15	
Age continuous			
Birthyear is documented. Day and month are set to July 1st to get the birthdate. Age is calculated as floor of screening date minus birthdate.			
Units: years			
arithmetic mean	62.2		
full range (min-max)	32 to 78	-	
Gender categorical			
Gender is documented on the CRF			
Units: Subjects			
Female	9	9	
Male	31	31	
Ethnic Origin			
Ethnic Origin is documented on the CRF			
Units: Subjects			
Caucasian/white	38	38	
Black	0	0	
Oriental/asian	2	2	
Other	0	0	
BMI			
Height and weight is documented at baseline.			
Units: Subjects			
underweight	1	1	
Normal weight	18	18	
overweight	14	14	
obese	7	7	
Hepatic metastasis Units: Subjects			
no	6	6	
yes	34	34	
Pulmonal metastasis Units: Subjects			
no	30	30	

yes	10	10	
Other metastasis Units: Subjects			
no	27	27	
yes	13	13	
pTNM Classification: Tumor Units: Subjects			
T1	3	3	
T3	24	24	
T4	5	5	
T4a	1	1	
T?	2	2	
Tc4	2	2	
Tx	2	2	
Typ3	1	1	
pTNM Classification: Metastasis Units: Subjects			
M0	10	10	
M1	25	25	
M?	1	1	
Mc1	2	2	
Mx	2	2	
pTNM Classification: Nodes Units: Subjects			
N0	8	8	
N1	11	11	
N2	9	9	
N2b	4	4	
N?	2	2	
Nc+	1	1	
Nx	3	3	
Nyp0	1	1	
Nc1	1	1	
pTNM Classification Units: Subjects			
T1N0M1	1	1	
T1N1M1	1	1	
T1NxMx	1	1	
T3N0M0	3	3	
T3N0M1	2	2	
T3N1M1	5	5	
T3N1Mx	1	1	
T3N2M0	3	3	
T3N2M1	4	4	
T3N2bM0	1	1	
T3N2bM1	2	2	
T4N0M1	2	2	
T4N1M1	1	1	
T4N2M1	2	2	
T4aN2bM1	1	1	
T?N?M1	1	1	

T?N?M?	1	1	
Tc4Nc1Mc1	1	1	
Tc4Nc+Mc1	1	1	
TxNxM1	2	2	
Typ3Nyp0M1	1	1	
T3N1M0	3	3	
Grading Units: Subjects			
Missing	4	4	
One	1	1	
Two	25	25	
Three	10	10	
KRAS status Units: Subjects			
Wild-Type	40	40	
Mutant	0	0	
Missing	0	0	
KRAS Exon 2 Codon 13 or 13 Units: Subjects			
Wild-Type	35	35	
Mutant	0	0	
Missing	5	5	
KRAS Exon 3 Codon 61 Units: Subjects			
Missing	5	5	
Wild-Type	34	34	
Mutant	1	1	
KRAS Exon 4 Codon 117 or 146 Units: Subjects			
Missing	6	6	
Wild-Type	32	32	
Mutant	2	2	
NRAS Exon 2 Codon 12 or 13 Units: Subjects			
Missing	6	6	
Wild-Type	33	33	
Mutant	1	1	
NRAS Exon 3 Codon 61 Units: Subjects			
Missing	6	6	
Wild-Type	33	33	
Mutant	1	1	
NRAS Exon 4 Codon 117 or 146 Units: Subjects			
Missing	6	6	
Wild-Type	34	34	
Mutant	0	0	
Site of primary tumor Units: Subjects			
Colon	18	18	
Rectum	20	20	

More than one site	2	2	

BMI			
Units: kg/m^2			
arithmetic mean	25.4		
full range (min-max)	17.2 to 34.6	-	

Subject analysis sets

Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Set includes all study patients who received any amount of cetuximab.

Subject analysis set title	Analysis Set 1
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All study patients for whom the variable ΔSUV as well as the response measurement is available and who are of KRAS-wt gene status. Patients dying from tumor progression before day 56 were regarded as clinical non-responders and included in the analysis of the primary endpoint. This set is used for analysis of the primary endpoint.

Subject analysis set title	Analysis Set 2
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All patients whose tumors are of RAS-wt gene status. This set is used for the analysis of secondary endpoints clinical response rate, PFS and OS. The analysis of clinical rsponse is restricted to patients for whom response on day 56 was determined.

Reporting group values	Safety Set	Analysis Set 1	Analysis Set 2
Number of subjects	40	33	28
Age categorical			
Birthyear is documented. Day and month are set to July 1st to get the birthdate. Age is calculated as floor of screening date minus birthdate.			
Units: Subjects			
From 18 to 44	1	1	1
From 45 to 65	24	20	17
>=65	15	12	10
Age continuous			
Birthyear is documented. Day and month are set to July 1st to get the birthdate. Age is calculated as floor of screening date minus birthdate.			
Units: years			
arithmetic mean	62.2	61.2	61.3
full range (min-max)	32 to 78	32 to 76	32 to 76
Gender categorical			
Gender is documented on the CRF			
Units: Subjects			
Female	9	7	7
Male	31	26	21
Ethnic Origin			
Ethnic Origin is documented on the CRF			
Units: Subjects			

Caucasian/white	38	31	26
Black	0	0	0
Oriental/asian	2	2	2
Other	0	0	0
BMI			
Height and weight is documented at baseline.			
Units: Subjects			
underweight	1	1	1
Normal weight	18	17	13
overweight	14	10	9
obese	7	5	5
Hepatic metastasis Units: Subjects			
no	6	5	3
yes	34	28	25
Pulmonal metastasis Units: Subjects			
no	30	26	21
yes	10	7	7
Other metastasis Units: Subjects			
no	27	25	19
yes	13	8	9
pTNM Classification: Tumor Units: Subjects			
T1	3	3	2
T3	24	20	16
T4	5	5	5
T4a	1	1	1
T?	2	2	2
Tc4	2	1	1
Tx	2	1	1
Typ3	1	0	0
pTNM Classification: Metastasis Units: Subjects			
M0	10	8	6
M1	25	21	18
M?	1	1	1
Mc1	2	1	1
Mx	2	2	2
pTNM Classification: Nodes Units: Subjects			
N0	8	7	5
N1	11	10	9
N2	9	7	5
N2b	4	4	4
N?	2	2	2
Nc+	1	0	0
Nx	3	2	2
Nyp0	1	0	0
Nc1	1	1	1

pTNM Classification Units: Subjects			
T1N0M1	1	1	1
T1N1M1	1	1	0
T1NxMx	1	1	1
T3N0M0	3	2	2
T3N0M1	2	2	0
T3N1M1	5	4	5
T3N1Mx	1	1	1
T3N2M0	3	2	1
T3N2M1	4	3	2
T3N2bM0	1	1	1
T3N2bM1	2	2	2
T4N0M1	2	2	2
T4N1M1	1	1	1
T4N2M1	2	2	2
T4aN2bM1	1	1	1
T?N?M1	1	1	1
T?N?M?	1	1	1
Tc4Nc1Mc1	1	1	1
Tc4Nc+Mc1	1	0	0
TxNxM1	2	1	1
Typ3Nyp0M1	1	0	0
T3N1M0	3	3	2
Grading Units: Subjects			
Missing	4	4	3
One	1	1	1
Two	25	19	16
Three	10	9	8
KRAS status Units: Subjects			
Wild-Type	40	33	28
Mutant	0	0	0
Missing	0	0	0
KRAS Exon 2 Codon 13 or 13 Units: Subjects			
Wild-Type	35	32	28
Mutant	0	0	0
Missing	5	1	0
KRAS Exon 3 Codon 61 Units: Subjects			
Missing	5	1	0
Wild-Type	34	31	28
Mutant	1	1	0
KRAS Exon 4 Codon 117 or 146 Units: Subjects			
Missing	6	2	0
Wild-Type	32	29	28
Mutant	2	2	0
NRAS Exon 2 Codon 12 or 13			

Units: Subjects			
Missing	6	2	0
Wild-Type	33	33	28
Mutant	1	1	0
NRAS Exon 3 Codon 61 Units: Subjects			
Missing	6	2	0
Wild-Type	33	31	28
Mutant	1	0	0
NRAS Exon 4 Codon 117 or 146 Units: Subjects			
Missing	6	2	0
Wild-Type	34	31	28
Mutant	0	0	0
Site of primary tumor Units: Subjects			
Colon	18	15	11
Rectum	20	17	15
More than one site	2	1	2
BMI Units: kg/m^2			
arithmetic mean	25.4	24.8	25.1
full range (min-max)	17.2 to 34.6	17.2 to 34.6	17.2 to 34.6

End points

End points reporting groups

Reporting group title	Single Arm: Treatment with Cetuximab
Reporting group description: -	
Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Set includes all study patients who received any amount of cetuximab.	
Subject analysis set title	Analysis Set 1
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All study patients for whom the variable ΔSUV as well as the response measurement is available and who are of KRAS-wt gene status. Patients dying from tumor progression before day 56 were regarded as clinical non-responders and included in the analysis of the primary endpoint. This set is used for analysis of the primary endpoint.	
Subject analysis set title	Analysis Set 2
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All patients whose tumors are of RAS-wt gene status. This set is used for the analysis of secondary endpoints clinical response rate, PFS and OS. The analysis of clinical rsponse is restricted to patients for whom response on day 56 was determined.	

Primary: Clinical Response

End point title	Clinical Response
End point description:	
The primary endpoint is clinical response. Responders are defined as patients achieving partial (PR) or complete response (CR) as measured by RECIST with a routine CT scan on day 56 in comparison with the baseline analysis. The primary objective of this study was to evaluate the prognostic relevance of relative changes in SUV (as measured in 18F-FDG PET-CT at day 14 versus baseline) for early clinical response (as defined by RECIST, measured at day 56) during short-term single agent treatment with the EGFR-mAB cetuximab. Cetuximab was administered during a two week treatment phase, and the 18F-FDG PET-CT analysis was conducted at baseline and day 14.	
End point type	Primary
End point timeframe:	
Baseline compared to day 56	

End point values	Analysis Set 1	Analysis Set 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	33	28		
Units: integer				
Missing	0	1		
Non-Responder (SD, PD)	14	11		
Responder (CR, PR)	19	16		

Statistical analyses

Statistical analysis title	Wilcoxon rank-sum test

Statistical analysis description:

The Wilcoxon rank-sum test was used to test the null hypothesis that ΔSUV has no predictive power for early clinical response (i.e. the distribution of ΔSUV is the same for non-responders vs. responders).

Comparison groups	Analysis Set 1
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	equivalence[1]
P-value	= 0.0092 [2]
Method	Wilcoxon rank-sum test

Notes:

[1] - The test statistic indicated that the ΔSUV for responders was significantly higher than for the group of non-responders. The distribution of ranks was found to differ significantly between both groups. Therefore, the null hypothesis that the distribution of ΔSUV in the groups of early clinical responders and non-responders is identical could be rejected at the 5% significance level.
[2] - Two-sided, normal approximation;

Secondary: Clinical Response Rate

End point title	Clinical Response Rate

End point description:

End point type	Secondary

End point timeframe:

Baseline compared to day 56

End point values	Analysis Set 2			
Subject group type	Subject analysis set			
Number of subjects analysed	27[3]			
Units: decimal				
number (not applicable)				
non-Responder	0.407			
Responder	0.593			

Notes:

[3] - One patient of analysis set 2 was excluded because of missing information

Statistical analyses

No statistical analyses for this end point

Secondary: PFS

End point title	PFS

End point description:

Progression-free survival (PFS), defined as the time from admission to the study to objective tumor progression or death from any cause, whichever occurs first. Times were censored by the duration of follow-up.

End point type	Secondary

End point timeframe:

From FPFV to overall EOS

End point values	Analysis Set 2			
Subject group type	Subject analysis set			
Number of subjects analysed	28			
Units: decimel				
number (confidence interval 95%)				
25 Percent Point Estimate	6.6 (2.1 to 10.2)			
Median	11.7 (7.3 to 15.0)			
75 Percent Point Estimate	17.2 (13.0 to -)			
1-year event-free rate	0.444 (0.256 to 0.617)			

Statistical analyses

No statistical analyses for this end point

Secondary: OS

End point title	OS

End point description:

Overall survival (OS), defined as the time from admission to the study to death from any cause. Times were censored by the duration of follow-up.

End point type	Secondary

End point timeframe:

From FPFV to overall EOS

End point values	Analysis Set 2			
Subject group type	Subject analysis set			
Number of subjects analysed	28			
Units: decimal				
number (confidence interval 95%)				
25 Percent Point Estimate	19.7 (5.2 to 24.6)			
Median	36.4 (21.1 to 50.5)			
75 Percent Point Estimate	50.5 (38.6 to -)			
1-year event free rate	0.889 (0.694 to 0.963)			

Statistical analyses

No statistical analyses for this end point

Secondary: Antivascular/Antiangiogenic Effects

End point title	Antivascular/Antiangiogenic Effects

End point description:

The absolute and relative change from baseline to day 14 in the following variables describing the results assessment of antivascular/antiangiogenic effects of cetuximab by CEUS: SImax, Time from start of application to flash, Regional blood volume (RBV), Regional blood flow (RBF).

End point type	Secondary

End point timeframe:

baseline and day 14

End point values	Analysis Set 2			
Subject group type	Subject analysis set			
Number of subjects analysed	28			
Units: decimal				
median (full range (min-max))				
SI max (%) for responder=no, baseline	23.0 (12.0 to 27.0)			
SI max (%) for responder=yes, baseline	19.0 (15.0 to 50.0)			
SI max (%) for responser=no, day 14	19.0 (11.0 to 30.0)			
SI max (%) for responder=yes, day 14	20.5 (12.0 to 47.0)			
SI max (%) for responder=no, abs. change	3.0 (-15.0 to 12.0)			
SI max (%) for responder=yes, abs. change	7.0 (-22.0 to 19.0)			
SI max (%) for responder=no, rel. change	11.1 (-100.0 to 52.2)			
SI max (%) for responder=yes, rel. change	24.3 (-88.0 to 60.0)			
Time to flash (s) for responder=no, baseline	3.0 (3.0 to 3.1)			
Time to flash (s) for responder=yes, baseline	3.1 (3.0 to 180.0)			
Time to flash (s) for responder=no, day 14	3.1 (2.0 to 3.1)			
Time to flash (s) for responder=yes, day 14	3.2 (3.0 to 3.9)			
Time to flash (s) for responder=no, abs. change	0.0 (-0.1 to 1.0)			
Time to flash (s) for responder=yes, abs. change	0.0 (-0.2 to 176.1)			
Time to flash (s) for responder=no, rel. change	0.7 (-3.0 to 33.8)			
Time to flash (s) for responder=yes, rel. change	-1.3 (-5.2 to 97.8)			
RBV for responder=no, baseline	8.5 (4.6 to 16.9)			
RBV for responder=yes, baseline	14.4 (5.2 to 27.8)			
RBV for responder=no, day 14	9.6 (3.8 to 19.3)			

RBV for responder=yes, day 14	11.2 (8.6 to 33.9)			
RBV for responder=no, abs. change	-1.8 (-10.8 to 6.8)			
RBV for responder=yes, abs. change	3.1 (-22.5 to 16.0)			
RBV for responder=no, rel. change	-39.1 (-127.1 to 64.2)			
RBV for responder=yes, rel. change	9.9 (-197.4 to 65.0)			
RBF for responder=no, baseline	0.9 (0.3 to 2.5)			
RBF for responder=yes, baseline	1.7 (0.4 to 4.7)			
RBF for responder=no, day 14	2.3 (0.2 to 5.8)			
RBF for responder=yes, day 14	2.3 (0.0 to 25.9)			
RBF for responder=no, abs. change	-0.4 (-5.5 to 1.0)			
RBF for responder=yes, abs. change	-0.3 (-22.5 to 1.8)			
RBF for responder=no, rel. change	-46.8 (-1950.4 to 85.0)			
RBF for responder=yes, rel. change	-35.3 (-657.8 to 97.6)			

Statistical analyses

Statistical analysis title	Wilcoxon rank-sum test SI max (%) abs. change

Statistical analysis description:

The Wilcoxon signed rank test will be used to test differences in the endpoints from baseline to day 14 for statistical significance (SAS: proc univariate, applied to absolute differences). For each of the endpoints, the Wilcoxon rank sum test will be used to compare clinical responders vs. clinical non-responders with respect to the relative change from baseline to day 14.

Comparison groups	Analysis Set 2
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	equivalence[4]
P-value	= 0.699
Method	Wilcoxon rank-sum test

Notes:

[4] - Here the Wilcoxon rank-sum test for SI max and relative change is performed

Statistical analysis title	Wilcoxon rank-sum test SI max (%) rel. change

Statistical analysis description:

The Wilcoxon signed rank test will be used to test differences in the endpoints from baseline to day 14 for statistical significance (SAS: proc univariate, applied to absolute differences). For each of the endpoints, the Wilcoxon rank sum test will be used to compare clinical responders vs. clinical non-responders with respect to the relative change from baseline to day 14.

Comparison groups	
Number of subjects included in analysis	0
Analysis specification	Pre-specified
Analysis type	equivalence[5]
P-value	= 0.792
Method	Wilcoxon rank-sum test

Notes:

[5] - Here the Wilcoxon rank-sum test for SI max and relative change is performed

Statistical analysis title	Wilcoxon rank-sum test time to flash abs. change

Statistical analysis description:

The Wilcoxon signed rank test will be used to test differences in the endpoints from baseline to day 14 for statistical significance (SAS: proc univariate, applied to absolute differences). For each of the endpoints, the Wilcoxon rank sum test will be used to compare clinical responders vs. clinical non-responders with respect to the relative change from baseline to day 14.

Comparison groups	Analysis Set 2
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	equivalence[6]
P-value	= 0.567
Method	Wilcoxon rank-sum test

Notes:

[6] - Here the Wilcoxon rank-sum test for time to flash and absolute change is performed

Statistical analysis title	Wilcoxon rank-sum test time to flash rel. change

Statistical analysis description:

The Wilcoxon signed rank test will be used to test differences in the endpoints from baseline to day 14 for statistical significance (SAS: proc univariate, applied to absolute differences). For each of the endpoints, the Wilcoxon rank sum test will be used to compare clinical responders vs. clinical non-responders with respect to the relative change from baseline to day 14.

Comparison groups	Analysis Set 2
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	equivalence[7]
P-value	= 0.662
Method	Wilcoxon rank-sum test

Notes:

[7] - Here the Wilcoxon rank-sum test for time to flash and relative change is performed

Statistical analysis title	Wilcoxon rank-sum test RBV abs. change

Statistical analysis description:

The Wilcoxon signed rank test will be used to test differences in the endpoints from baseline to day 14 for statistical significance (SAS: proc univariate, applied to absolute differences). For each of the endpoints, the Wilcoxon rank sum test will be used to compare clinical responders vs. clinical non-responders with respect to the relative change from baseline to day 14.

Comparison groups	Analysis Set 2
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	equivalence[8]
P-value	= 0.537
Method	Wilcoxon rank-sum test

Notes:

[8] - Here the Wilcoxon rank-sum test for RBV and absolute change is performed

Statistical analysis title	Wilcoxon rank-sum test RBV rel. change

Statistical analysis description:

The Wilcoxon signed rank test will be used to test differences in the endpoints from baseline to day 14 for statistical significance (SAS: proc univariate, applied to absolute differences). For each of the

endpoints, the Wilcoxon rank sum test will be used to compare clinical responders vs. clinical non-responders with respect to the relative change from baseline to day 14.

Comparison groups	Analysis Set 2
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	equivalence[9]
P-value	= 0.931
Method	Wilcoxon rank-sum test

Notes:

[9] - Here the Wilcoxon rank-sum test for RBV and relative change is performed

Statistical analysis title	Wilcoxon rank-sum test RBF abs. change

Statistical analysis description:

The Wilcoxon signed rank test will be used to test differences in the endpoints from baseline to day 14 for statistical significance (SAS: proc univariate, applied to absolute differences). For each of the endpoints, the Wilcoxon rank sum test will be used to compare clinical responders vs. clinical non-responders with respect to the relative change from baseline to day 14

Comparison groups	Analysis Set 2
Number of subjects included in analysis	28
Analysis specification	
Analysis type	equivalence[10]
P-value	= 0.792
Method	Wilcoxon rank-sum test

Notes:

[10] - Here the Wilcoxon rank-sum test for RBF and absolute change is performed

Statistical analysis title	Wilcoxon rank-sum test RBF rel. change

Statistical analysis description:

The Wilcoxon signed rank test will be used to test differences in the endpoints from baseline to day 14 for statistical significance (SAS: proc univariate, applied to absolute differences). For each of the endpoints, the Wilcoxon rank sum test will be used to compare clinical responders vs. clinical non-responders with respect to the relative change from baseline to day 14

Comparison groups	Analysis Set 2
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	equivalence[11]
P-value	= 0.931
Method	Wilcoxon rank-sum test

Notes:

[11] - Here the Wilcoxon rank-sum test for RBF and relative change is performed

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline until day 56	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	Safety Set

Reporting group description:

The Safety Population included all study patients who received any amount of cetuximab, with the addition of adverse events that were recorded at baseline.

Serious adverse events	Safety Set		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 40 (12.50%)		
number of deaths (all causes)	24		
number of deaths resulting from adverse events	1		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ileus			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Infections and infestations			
Atypical pneumonia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Sepsis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Safety Set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 40 (92.50%)		
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Haematoma			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Hypotension			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		

Immune system disorders			
Hypersensitivity			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	5		

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	9 / 40 (22.50%)		
occurrences (all)	9		
Feeling hot			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Influenza like illness			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Malaise			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Mucosal inflammation			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Oedema peripheral			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Temperature intolerance			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Psychiatric disorders			
Aggression			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Anxiety			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Stoma complication			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		

Weight decreased subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Weight increased subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Investigations C-reactive protein increased subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Haemoglobin decreased subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Dysphonia subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 3		
Epistaxis subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Hiccups subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Pulmonary embolism subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Rhonchi subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		

Throat irritation subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Iron deficiency anaemia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all)	 2 / 40 (5.00%) 2 2 / 40 (5.00%) 2 2 / 40 (5.00%) 2		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Dysgeusia subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	 2 / 40 (5.00%) 2 1 / 40 (2.50%) 1 3 / 40 (7.50%) 3		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	 1 / 40 (2.50%) 1		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain lower subjects affected / exposed occurrences (all) Abdominal pain upperpper subjects affected / exposed occurrences (all)	 2 / 40 (5.00%) 2 1 / 40 (2.50%) 1 1 / 40 (2.50%) 1		

Aphthous ulcer				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Cheilitis				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Constipation				
subjects affected / exposed	4 / 40 (10.00%)			
occurrences (all)	4			
Diarrhoea				
subjects affected / exposed	17 / 40 (42.50%)			
occurrences (all)	17			
Dyspepsia				
subjects affected / exposed	2 / 40 (5.00%)			
occurrences (all)	2			
Flatulence				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Gastrointestinal pain				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Gastrooesophageal reflux disease				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Ileus				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Nausea				
subjects affected / exposed	6 / 40 (15.00%)			
occurrences (all)	6			
Pancreatitis				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Stomatitis				
subjects affected / exposed	4 / 40 (10.00%)			
occurrences (all)	4			

Vomiting			
subjects affected / exposed	6 / 40 (15.00%)		
occurrences (all)	6		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Pollakiuria			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Renal pain			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Alopecia			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Dry skin			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Hyperhidrosis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	6 / 40 (15.00%)		
occurrences (all)	6		
Rash			
subjects affected / exposed	8 / 40 (20.00%)		
occurrences (all)	8		
Skin fissures			
subjects affected / exposed	9 / 40 (22.50%)		

occurrences (all)	9		
Skin toxicity			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Dehydration			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Hyperglycaemia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Hypoglycaemia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Hypomagnesaemia			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Hyponatraemia			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Infections and infestations			
Atypical pneumonia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Herpes virus infection			
subjects affected / exposed	1 / 40 (2.50%)		

occurrences (all)	1		
Oral herpes			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Paronychia			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Sepsis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)			

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 July 2010	Amendment 01: New Protocol Version 1. 7 due to Change of PI (Anne Katrin Berger to Dirk Jäger)
14 October 2010	Amendment 05: new Protocol Version 1.8 including amendment 02-04 (New investigators: Christian Zechmann, Katharina Grünberg, Karl Roland Ehrenberg, Stephan Nachtigall, Klaus Podar, Stefan Welte, Martin Schmitz)
09 May 2011	Amendment 08: new Protocol Version 1.9 including amendment 06-07 (New investigators Mareike Dietrich, Sonia Vallet, Change of PI (Dirk Jäger to Anne Katrin Berger))
27 July 2011	Amendment 09: new Protocol Version 1.10 due to amended exclusion criteria
20 February 2014	Amendment 14: new Protocol Version 1.11 due to Change of Inclusion criterion (only KRAS and NRAS wildtype patients to be included) due to new scientific findings; including amendment 11-13 (New Summary of Product Characteristics (Date October 2011, New investigator Annika Stange, Updated Patient Informed Consent to add information about Federal Office for Radiation Protection in the Data Protection Section)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported