Clinical trial results:
Phase I/II-study of hyperfractionated-accelerated radiation therapy (HART) plus cetuximab (CET) plus cisplatin (CIS) chemotherapy in locally advanced inoperable squamous cell cancers of head and neck.

Summary

EudraCT number	2005-000355-15
Trial protocol	DE
Global end of trial date	10 March 2016

Results information

Result version number	v1 (current)
This version publication date	12 May 2021
First version publication date	12 May 2021
Summary attachment (see zip file)	Final Study Report (Final Study Report HART-CIS-CET-V01F_2016-11-25.pdf)

Trial information

Trial identification

Sponsor protocol code	KKSH-19

Additional study identifiers

ISRCTN number	ISRCTN47339346
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Martin-Luther-Universität Halle-Wittenberg
Sponsor organisation address	Magdeburger Str. 8, Halle (Saale), Germany, 06112
Public contact	Koordinierungszentrum für Klinische Studien, Martin-Luther-Universität Halle-Wittenberg, +49 3455574903, info@kks-halle.de
Scientific contact	Koordinierungszentrum für Klinische Studien, Martin-Luther-Universität Halle-Wittenberg, +49 3455574903, info@kks-halle.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	01 June 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Determination of feasibility, efficacy and safety of cetuximab (CET) combined with cisplatin (CIS) and hyperfractionated, accelerated radiotherapy (HART) as a treatment option with curative intent for patients with locally advanced, unresectable SCCHN.
Phase I: defining the maximum tolerated dose (MTD) of a short infusion of cisplatin in the combined-modality treatment with cetuximab
Phase II: Efficacy of combined-modality treatment with regards to progression-free survival. The dose of cisplatin in this combined-modality treatment was determined in phase I.

Protection of trial subjects:

- Antiemetic treatment according to local clinical standard.
- In case of leucopenia or fever a supportive antibiotic treatment according to institutional standard has been used dependend on microbiological testing.
- Intensive care of the oral cavity (mucositis prophylaxis) with iodine solution and/or dexpanthenol solution with or without antifungal agents and analgetic treatment was done if required.
- Skin toxicity due to cetuximab were treated, if necessary with topical and oral antibiotics.
- Radiation-induced skin toxicity were treated with ointment (e.g. Bepanthen®), if necessary with topical corticosteroids.
- If clinically indicated transfusion of blood products (erythrocytes or platelets) has been performed.
- During radiotherapy an adequate nutrition has been provided. If necessary, a supplementary, high-caloric nutrition was done by using the PEG.

Background therapy:

Antiemetic treatment according to local clinical standard.
During radiotherapy an adequate nutrition has been provided.

Evidence for comparator:

No comparator was used-

Actual start date of recruitment	14 September 2005
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: 88
Worldwide total number of subjects	88
EEA total number of subjects	88

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)	83
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between 14/09/2005 and 22/02/2008, 18 patients were enrolled in phase I study according to dose escalation scheme -- 3, 5, 3 and 7 patients at dose level 1, 2, 3 and 4, respectively. Between 07/04/2008 and 01/09/2010, 70 patients were recruited in phase II study at dose level 4. All patients were recruited at 7 trial sites in Germany.

Pre-assignment

Screening details:

Each patient considered by the Investigator to be a potential patient for the study underwent the informed consent process. If the patient agreed to participate in the study and an informed consent form was duly completed, dated and signed, then the Investigator assessed the patient's eligibility for the study.

Period 1

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

Arms

Arm title	HART-CIS-CET

Arm description:

Subjects received a therapy consisting of Radiotherapy (HART), Cisplatin (CIS) and Cetuximab (CET). In phase I, the maximum tolerated dose (MTD) for escalated cisplatin in combination with cetuximab and radiotherapy was determined. In phase II therapy was performed with cisplatin at this recommended dose level and with the schedule of cetuximab and radiotherapy as described below.
HART: 30 Gy/2 Gy once daily, then twice daily 1.4 Gy to a total dose of 70.6 Gy, five days per week.
CET: loading dose 400 mg/sqm on day -7 followed by subsequent weekly doses of 250 mg/sqm on week 1 to 6 on days 1, 8, 15, 22, 29, 36
CIS: Phase I: escalating doses (20, 30, 35, 40 mg/sqm), once weekly, week 1 to 6 on days 1, 8, 15, 22, 29, 36 five days per week. Subjects were enrolled according to a dose escalating scheme described under Products --> Cisplatin.
CIS: Phase II: 40 mg/sqm, once weekly, week 1 to 6 on days 1, 8, 15, 22, 29, 36

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

Dosage and administration details:

Phase I: dose according to escalating scheme (20, 30, 35, 40 mg/m²), once weekly on week 1 to 6 over a 1-hour i.v. infusion on days 1, 8, 15, 22, 29, 36.
3 patients entered at the first dose level of cisplatin. If no Dose Limiting Toxicity (DLT) occur, 3 patients entered at the next dose level. If 1 out of 3 patients at any dose level experiences DLT, 3 additional patients were treated at the same dose level, up to 6 patients were treated at that dose level. If no additional DLT ocurred, the dose escalation were proceeded. If 2 of 3 or 2 of 6 patients experience DLT, the dose was considered to be above the Maximum tolerated dose (MTD) and escalation ended. MTD was defined as dose level of cisplatin below the maximally administered dose at which 0 of 3 or not more than 1 of 6 patients experience DLT. The MTD (here 40 mg/sqm) was the recommended phase II dose level of cisplatin.
Phase II: 40 mg/m², once weekly on week 1 to 6 over a 1-hour i.v. infusion on days 1, 8, 15, 22, 22, 29, 36

Investigational medicinal product name	Erbitux
Investigational medicinal product code	CET
Other name	
Pharmaceutical forms	Solution for infusion

Routes of administration	Intravenous use

Dosage and administration details:

Erbitux was scheduled to be administered once weekly with an initial dose of 400 mg/m² body surface cetuximab (= loading dose at week -1) followed by subsequent weekly doses of 250 mg/m² (week 1–6) on days 1, 8, 15, 22, 29, 36. The loading dose was administered 7 days before initiation of radio- and chemotherapy period. Prior to the first administration of cetuximab, patients were premedicated with an antihistamine. This premedication was also recommended prior to all subsequent infusions of cetuximab.

Number of subjects in period 1	HART-CIS-CET
Started	88
Completed	76
Not completed	12
Consent withdrawn by subject	1
Screening failure	3
Lost to follow-up	2
Exclusion criterion: Metastatic disease	1
Exclusion crit.: Another cancer within 5 year	1
Serious concomitant disease or medical condition	3
Did not receive study treatment	1

Baseline characteristics

Reporting groups	
Reporting group title	HART-CIS-CET overall study
Reporting group description:	
All subjects initially enroled. Includes dropouts and subjects who did not receive study treatment or subjects who were subsequently excluded from the endpoint analysis for any reason.	

Reporting group values	HART-CIS-CET overall study	Total	
Number of subjects	88	88	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	83	83	
From 65-84 years	5	5	
85 years and over	0	0	
not determined/missing	0	0	
Age continuous Units: years			
median	55		
full range (min-max)	37 to 69	-	
Gender categorical Units: Subjects			
Female	13	13	
Male	75	75	
Smoking habits Units: Subjects			
Non-smoker	4	4	
Ex-smoker	33	33	
Smoker	32	32	
Unknown	19	19	
Tumor characteristics - localisation of primary tumor Units: Subjects			
Oral cavity	8	8	
Oropharynx	38	38	
Hypopharynx	21	21	
Larynx	11	11	
Unknown	10	10	
Tumor characteristics - pathological staging - T-status Units: Subjects			
T1	0	0	

T2	7	7	
T3	18	18	
T4a	44	44	
T4b	8	8	
Unknown	11	11	
Tumor characteristics - pathological staging - N status Units: Subjects			
N1	5	5	
N2	59	59	
N3	11	11	
Unknown	13	13	
Tumor characteristics - pathological staging - M status Units: Subjects			
M0	77	77	
M1	1	1	
Mx	0	0	
Unknown	10	10	
Tumor characteristics - pathological staging Units: Subjects			
III	6	6	
IVa	55	55	
IVb	17	17	
IVc	0	0	
Unknown	10	10	
Tumor characteristics - resectability Units: Subjects			
Resectable	10	10	
Not resectable	68	68	
Unknown	10	10	
Tumor characteristics - histopathological grading Units: Subjects			
G1	3	3	
G1/2	2	2	
G2	50	50	
G2/3	2	2	
G3	17	17	
G3/4	0	0	
G4	0	0	
Gx	2	2	
Unknown	12	12	
Karnofsky performance status, n=71 Units: percent (%)			
median	90		
full range (min-max)	50 to 100	-	

End points

End points reporting groups

Reporting group title	HART-CIS-CET

Reporting group description:

Subjects received a therapy consisting of Radiotherapy (HART), Cisplatin (CIS) and Cetuximab (CET). In phase I, the maximum tolerated dose (MTD) for escalated cisplatin in combination with cetuximab and radiotherapy was determined. In phase II therapy was performed with cisplatin at this recommended dose level and with the schedule of cetuximab and radiotherapy as described below.
HART: 30 Gy/2 Gy once daily, then twice daily 1.4 Gy to a total dose of 70.6 Gy, five days per week.
CET: loading dose 400 mg/sqm on day -7 followed by subsequent weekly doses of 250 mg/sqm on week 1 to 6 on days 1, 8, 15, 22, 29, 36
CIS: Phase I: escalating doses (20, 30, 35, 40 mg/sqm), once weekly, week 1 to 6 on days 1, 8, 15, 22, 29, 36 five days per week. Subjects were enrolled according to a dose escalating scheme described under Products --> Cisplatin.
CIS: Phase II: 40 mg/sqm, once weekly, week 1 to 6 on days 1, 8, 15, 22, 29, 36

Subject analysis set title	Phase I per-protocol (PP)
Subject analysis set type	Per protocol

Subject analysis set description:

In phase I study, the per-protocol (PP) analysis set consisted of those 15 patients, 3/3/3/6 at dose levels 1/2/3/4, who received the complete study medication, except in case of prior termination due to toxicity.

Subject analysis set title	Phase II Intention-to-treat (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

In phase II study, analysis sets were composed of the actual phase II patients and the phase I patients of dose level 4. Those 65 patients with informed consent, without metastatic disease and with outcome data on survival status and progression of disease were included in the intention-to-treat (ITT) analysis set.

Subject analysis set title	Phase II per-protocol (PP)
Subject analysis set type	Per protocol

Subject analysis set description:

Per-protocol patients were those 40 patients without inclusion/ exclusion exceptions who received at least 80% of the planned radiation and chemotherapy dose, i.e. at least 5 of 6 visits without dose modification of cetuximab and cisplatin, and at least 35 days radiotherapy regarding CTV I with no more than 14 days of interruption and at least 56.48 Gy (80% of 70.6 Gy) total dose and hyperfractionation according to treatment plan (or concomitant boost), without consideration of reason for dose modification or interruption.

Primary: Phase I: Dose limiting toxicities (DLTs)

End point title	Phase I: Dose limiting toxicities (DLTs)[1]

End point description:

Primary endpoint of phase I was the definition of maximum tolerated dose (MTD) of cisplatin in the proposed combined-modality treatment regimen. MTD was defined as dose level of cisplatin below the maximally administered dose at which zero of three or at most one of six patients experience dose limiting toxicities (DLT). The MTD was the recommended phase II dose level of cisplatin. If the MTD was not reached at the dose level 4 (40 mg/m² Cisplatin), this level would be recommended for phase II. DLT was defined as any grade 3 or higher toxicity (considered related to HART-CIS-CET) as determined by CTCAE, version 3.0. Also a hearing loss > grade 2 was considered as DLT. Excluded from the definition of DLT were grade 3 mucositis, infection with normal ANC or grade 1 to 3 neutrophils, hematologic or hepatic toxicity grade 3, alopecia (all grades). For toxicity within the irradiated volume, only grade 4 mucosal or skin toxicities, xerostomia and dysphagia were considered as DLTs.

End point type	Primary

End point timeframe:

at end of Phase I

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: Maximum tolerated dose (MTD) was defined as dose level of cisplatin below the maximally administered dose at which zero of three or at most one of six patients experience dose limiting toxicities (DLT).

The number of dose limiting toxicities (DLT) per dose level were counted to determine maximum tolerated dose (MTD). Therefore no statistical analysis was performed.

End point values	HART-CIS-CET	Phase I per-protocol (PP)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	15	15		
Units: Subjects				
No	0	0		
Yes	15	15		

Statistical analyses

No statistical analyses for this end point

Primary: Phase II: 2-year PFSR with lower confidence limit (CL) of one-sided 95% CI

End point title	Phase II: 2-year PFSR with lower confidence limit (CL) of one-sided 95% CI

End point description:

Primary endpoint of the phase II is the determination of progression-free survival (PFS), as measured by the 2-year progression-free survival rate. The progression-free survival rate is defined as the percentage of patients alive and without tumor progression at 2-years after start of treatment. If a patient has not progressed or died, progression-free survival is censored at the time of last follow-up. Progression of disease is defined according to RECIST as at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter since the treatment started or the appearance of one or more new lesions. In addition, subsequent head and neck primary or neck/ lymph node recurrence or newly diagnosed distant metastasis or any second primary tumor outside of the head and neck region will be considered as disease progression.

End point type	Primary

End point timeframe:

2 years after start of study treatment

End point values	Phase II Intention-to-treat (ITT)	Phase II per-protocol (PP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	65	40		
Units: Subjects				
number (not applicable)				
2-year PFSR	0.453	0.567		
Lower CL of one-sided 95% CI	0.346	0.427		
n Event	34	17		
n Censored	4	1		
n at Risk	27	22		

Statistical analyses

Statistical analysis title	ITT: 2-year progression-free survival rate

Statistical analysis description:

2-year progression-free survival rate (PFSR) and its one-sided 95% confidence interval (CI) was computed using Kaplan-Meier method. This corresponds with a one-sided binomial test with a significance level of α=0.05 and statistical hypotheses H0: PFSR≤0.40 vs. H1: PFSR>0.40.

Comparison groups	Phase II Intention-to-treat (ITT) v Phase II per-protocol (PP)
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority[2]
Parameter estimate	Rate
Point estimate	0.453
Confidence interval	
level	95 %
sides	1-sided
lower limit	0.346

Notes:

[2] - one-sided 95% confidence interval, H0: PFSR≤0.40 vs. H1: PFSR>0.40

Statistical analysis title	PP: 2-year progression-free survival rate

Statistical analysis description:

2-year progression-free survival rate (PFSR) and its one-sided 95% confidence interval (CI) was computed using Kaplan-Meier method. This corresponds with a one-sided binomial test with a significance level of α=0.05 and statistical hypotheses H0: PFSR≤0.40 vs. H1: PFSR>0.40.

Comparison groups	Phase II per-protocol (PP) v Phase II Intention-to-treat (ITT)
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority[3]
Parameter estimate	Rate
Point estimate	0.567
Confidence interval	
level	95 %
sides	1-sided
lower limit	0.427

Notes:

[3] - one-sided 95% confidence interval, H0: PFSR≤0.40 vs. H1: PFSR>0.40

Secondary: 1-, 2- and 5-year progression-free survival

End point title	1-, 2- and 5-year progression-free survival

End point description:

Time to progression is defined to be the time between start of treatment to the first observation of disease progression or death due to any cause. If a patient has not progressed or died, progression-free survival is censored at the time of last follow-up. The progression-free survival rate is defined as the percentage of patients alive and without tumor progression at 1-, 2- or 5-years after start of treatment. Progression of disease is defined according to RECIST as at least a 20% increase in the sum of the

longest diameter of target lesions, taking as reference the smallest sum longest diameter since the treatment started or the appearance of one or more new lesions. In addition, subsequent head and neck primary or neck/ lymph node recurrence or newly diagnosed distant metastasis or any second primary tumor outside of the head and neck region will be considered as disease progression.

End point type	Secondary

End point timeframe:

1-, 2- or 5-years after start of treatment

End point values	Phase II Intention-to-treat (ITT)	Phase II per-protocol (PP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	65	40		
Units: Rate				
number (confidence interval 95%)				
1- year PFS	0.567 (0.435 to 0.679)	0.670 (0.500 to 0.813)		
2-year PFS	0.453 (0.326 to 0.571)	0.567 (0.398 to 0.707)		
5-year PFS	0.323 (0.207 to 0.444)	0.392 (0.236 to 0.546)		

Attachments (see zip file)	PFS Kaplan-Meier estimate with pointwise 95%

Statistical analyses

Statistical analysis title	ITT: 1-year progression-free survival rate

Statistical analysis description:

1-year progression-free survival rate was estimated by Kaplan-Meier estimate and presented with two-sided 95% CI.

Comparison groups	Phase II Intention-to-treat (ITT) v Phase II per-protocol (PP)
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Rate
Point estimate	0.567
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.435
upper limit	0.679

Statistical analysis title	PP: 1-year progression-free survival rate

Statistical analysis description:

1-year progression-free survival rate was estimated by Kaplan-Meier estimate and presented with two-sided 95% CI.

Comparison groups	Phase II per-protocol (PP) v Phase II Intention-to-treat (ITT)

Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Rate
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	0.793

Statistical analysis title	ITT: 2-year progression-free survival rate

Statistical analysis description:

2-year progression-free survival rate was estimated by Kaplan-Meier estimate and presented with two-sided 95% CI.

Comparison groups	Phase II Intention-to-treat (ITT) v Phase II per-protocol (PP)
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Rate
Point estimate	0.453
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.326
upper limit	0.571

Statistical analysis title	ITT: 5-year progression-free survival rate

Statistical analysis description:

5-year progression-free survival rate was estimated by Kaplan-Meier estimate and presented with two-sided 95% CI.

Comparison groups	Phase II Intention-to-treat (ITT) v Phase II per-protocol (PP)
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Rate
Point estimate	0.323
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.207
upper limit	0.444

Statistical analysis title	PP: 2-year progression-free survival rate

Statistical analysis description:

2-year progression-free survival rate was estimated by Kaplan-Meier estimate and presented with two-sided 95% CI.

Comparison groups	Phase II per-protocol (PP) v Phase II Intention-to-treat (ITT)
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Rate
Point estimate	0.567
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.398
upper limit	0.704

Statistical analysis title	PP: 5-year progression-free survival rate

Statistical analysis description:

5-year progression-free survival rate was estimated by Kaplan-Meier estimate and presented with two-sided 95% CI.

Comparison groups	Phase II per-protocol (PP) v Phase II Intention-to-treat (ITT)
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Rate
Point estimate	0.392
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.236
upper limit	0.546

Secondary: 1-, 2- and 5-year loco-regional progression-free survival

End point title	1-, 2- and 5-year loco-regional progression-free survival

End point description:

Loco-regional progression-free survival (LPFS) is defined to be the time between start of treatment to the first observation of local disease recurrence as defined above, or death due to any cause. If a patient has not progressed or died, progression-free survival is censored at the time of last follow-up. The loco-regional progression-free survival rate is defined as the percentage of patients alive and without a local disease recurrence at 1-, 2 or 5-years after start of treatment.

End point type	Secondary

End point timeframe:

1-, 2- or 5-years after start of treatment

End point values	Phase II Intention-to-treat (ITT)	Phase II per-protocol (PP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	65	40		
Units: Rate				
number (confidence interval 95%)				
1-year LPFS	0.599 (0.466 to 0.708)	0.694 (0.525 to 0.813)		
2-year LPFS	0.453 (0.326 to 0.571)	0.566 (0.397 to 0.704)		
5-year LPFS	0.333 (0.215 to 0.456)	0.382 (0.225 to 0.537)		

Attachments (see zip file)	LRPFS Kaplan-Meier estimate with pointwise 95%

Statistical analyses

Statistical analysis title	ITT: 1-year loco-regional PFSR

Statistical analysis description:

1-year loco-regional progression-free survival rate was estimated by Kaplan-Meier estimate and presented with two-sided 95% CI.

Comparison groups	Phase II Intention-to-treat (ITT) v Phase II per-protocol (PP)
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Rate
Point estimate	0.599
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.466
upper limit	0.708

Statistical analysis title	ITT: 2-year loco-regional PFSR

Statistical analysis description:

2-year loco-regional progression-free survival rate was estimated by Kaplan-Meier estimate and presented with two-sided 95% CI.

Comparison groups	Phase II Intention-to-treat (ITT) v Phase II per-protocol (PP)
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Rate
Point estimate	0.469
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.341
upper limit	0.586

Statistical analysis title	ITT: 5-year loco-regional PFSR
Statistical analysis description:	
5-year loco-regional progression-free survival rate was estimated by Kaplan-Meier estimate and presented with two-sided 95% CI.	
Comparison groups	Phase II Intention-to-treat (ITT) v Phase II per-protocol (PP)
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Rate
Point estimate	0.333
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.215
upper limit	0.456

Statistical analysis title	PP: 1-year loco-regional PFSR
Statistical analysis description:	
1-year loco-regional progression-free survival rate was estimated by Kaplan-Meier estimate and presented with two-sided 95% CI.	
Comparison groups	Phase II per-protocol (PP) v Phase II Intention-to-treat (ITT)
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Rate
Point estimate	0.694
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.525
upper limit	0.813

Statistical analysis title	PP: 2-year loco-regional PFSR
Statistical analysis description:	
2-year loco-regional progression-free survival rate was estimated by Kaplan-Meier estimate and presented with two-sided 95% CI.	
Comparison groups	Phase II per-protocol (PP) v Phase II Intention-to-treat (ITT)
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Rate
Point estimate	0.566

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.397
upper limit	0.704

Statistical analysis title	PP: 5-year loco-regional PFSR

Statistical analysis description:

5-year loco-regional progression-free survival rate was estimated by Kaplan-Meier estimate and presented with two-sided 95% CI.

Comparison groups	Phase II per-protocol (PP) v Phase II Intention-to-treat (ITT)
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Rate
Point estimate	0.382
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.225
upper limit	0.537

Secondary: 1-, 2- and 5-year overall survival

End point title	1-, 2- and 5-year overall survival

End point description:

Overall survival (OS) is defined to be the time between start of treatment and death or (if the patient didn’t die) the date of last contact for living patients (censored observation). The overall survival rates are defined as the proportion of patients who survive completely the respective observation interval (1- and 2-year).

End point type	Secondary

End point timeframe:

1-, 2- or 5-years after start of treatment

End point values	Phase II Intention-to-treat (ITT)	Phase II per-protocol (PP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	65	40		
Units: Rate				
number (confidence interval 95%)				
1-year OSR	0.792 (0.668 to 0.873)	0.822 (0.662 to 0.911)		
2-year OSR	0.644 (0.511 to 0.749)	0.742 (0.573 to 0.852)		
5-year OSR	0.411 (0.284 to 0.534)	0.487 (0.318 to 0.636)		

Attachments (see zip file)	OSR Kaplan-Meier estimate with pointwise 95%

Statistical analyses

Statistical analysis title	ITT: 1-year overall survival rate

Statistical analysis description:

1-year overall survival rate was estimated by Kaplan-Meier estimate and presented with two-sided 95% CI.

Comparison groups	Phase II Intention-to-treat (ITT) v Phase II per-protocol (PP)
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Rate
Point estimate	0.792
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.668
upper limit	0.873

Statistical analysis title	Copy of Overall survival rates

Statistical analysis description:

1-, 2- and 5-year overall survival rates were estimated by Kaplan-Meier estimates and presented with their two-sided 95% CIs.

Comparison groups	Phase II per-protocol (PP) v Phase II Intention-to-treat (ITT)
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Rate
Point estimate	0.453
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	0.7

Statistical analysis title	ITT: 2-year overall survival rate

Statistical analysis description:

2-year overall survival rate was estimated by Kaplan-Meier estimate and presented with two-sided 95% CI.

Comparison groups	Phase II Intention-to-treat (ITT) v Phase II per-protocol (PP)

Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Rate
Point estimate	0.644
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.511
upper limit	0.749

Statistical analysis title	ITT: 5-year overall survival rate

Statistical analysis description:

5-year overall survival rate was estimated by Kaplan-Meier estimate and presented with two-sided 95% CI.

Comparison groups	Phase II Intention-to-treat (ITT) v Phase II per-protocol (PP)
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Rate
Point estimate	0.411
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.284
upper limit	0.534

Statistical analysis title	PP: 1-year overall survival rate

Statistical analysis description:

1-year overall survival rate was estimated by Kaplan-Meier estimate and presented with two-sided 95% CI.

Comparison groups	Phase II per-protocol (PP) v Phase II Intention-to-treat (ITT)
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Rate
Point estimate	0.822
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.662
upper limit	0.911

Statistical analysis title	PP: 2-year overall survival rate

Statistical analysis description:

2-year overall survival rate was estimated by Kaplan-Meier estimate and presented with two-sided 95% CI.

Comparison groups	Phase II per-protocol (PP) v Phase II Intention-to-treat (ITT)
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Rate
Point estimate	0.742
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.573
upper limit	0.852

Statistical analysis title	PP: 5-year overall survival rate

Statistical analysis description:

5-year overall survival rate was estimated by Kaplan-Meier estimate and presented with two-sided 95% CI.

Comparison groups	Phase II per-protocol (PP) v Phase II Intention-to-treat (ITT)
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Rate
Point estimate	0.487
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.318
upper limit	0.636

Secondary: Objective tumor response rate

End point title	Objective tumor response rate

End point description:

The objective tumour response rate (ORR) is defined as the proportion of all patients, with either a complete or a partial overall response, who have received at least one dose of chemotherapy and / or radiation therapy and have their disease re-evaluated. First CT/ MRI –evaluation will be done at 8 weeks after completion of therapy.

End point type	Secondary

End point timeframe:

at end of treatment

End point values	Phase II Intention-to-treat (ITT)	Phase II per-protocol (PP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	65[4]	40[5]		
Units: Rate				
number (confidence interval 95%)				
p CR/PR	0.800 (0.682 to 0.889)	0.875 (0.732 to 0.958)		

Notes:

[4] - n CR/PR: 52

[5] - n CR/PR: 35

Statistical analyses

Statistical analysis title	ITT: Objective tumor response rate
Statistical analysis description: Objective tumor response rate with two-sided 95% CI	
Comparison groups	Phase II Intention-to-treat (ITT) v Phase II per-protocol (PP)
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Proportion
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.682
upper limit	0.889

Statistical analysis title	PP: Objective tumor response rate
Statistical analysis description: Objective tumor response rate with two-sided 95% CI	
Comparison groups	Phase II per-protocol (PP) v Phase II Intention-to-treat (ITT)
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Proportion
Point estimate	0.875
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.732
upper limit	0.958

Secondary: Distant metastasis-free survival status

End point title	Distant metastasis-free survival status

End point description:

Distant metastasis-free survival (DMFS) is defined to be the time from start of treatment to date of first observed distant metastasis or death. If a patient has not progressed or died, DMFS is censored at the time of last follow-up. DMFS rate is defined as the percentage of patients alive and without a distant metastasis at 1-, 2 or 5-years after start of treatment.

End point type	Secondary

End point timeframe:

1-, 2- or 5-years after start of treatment

End point values	Phase II Intention-to-treat (ITT)	Phase II per-protocol (PP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	65	40		
Units: Rate				
number (confidence interval 95%)				
1-year DMFSR	0.712 (0.582 to 0.808)	0.797 (0.635 to 0.893)		
2-year DMFSR	0.598 (0.465 to 0.708)	0.669 (0.498 to 0.792)		
5-year DMFSR	0.385 (0.261 to 0.507)	0.443 (0.279 to 0.594)		

Attachments (see zip file)	DMFS Kaplan-Meier estimate with pointwise 95%

Statistical analyses

Statistical analysis title	ITT: 1-year distant metastasis-free survival rate

Statistical analysis description:

1-year distant metastasis-free survival rate was estimated by Kaplan-Meier estimate and presented with two-sided 95% CI.

Comparison groups	Phase II Intention-to-treat (ITT) v Phase II per-protocol (PP)
Number of subjects included in analysis	105
Analysis specification	Post-hoc
Analysis type	other
Parameter estimate	Rate
Point estimate	0.712
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.582
upper limit	0.808

Statistical analysis title	ITT: 2-year distant metastasis-free sur...

Statistical analysis description:

2-year distant metastasis-free survival rate was estimated by Kaplan-Meier estimate and presented with

two-sided 95% CI.

Comparison groups	Phase II Intention-to-treat (ITT) v Phase II per-protocol (PP)
Number of subjects included in analysis	105
Analysis specification	Post-hoc
Analysis type	other
Parameter estimate	Rate
Point estimate	0.598
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.465
upper limit	0.708

Statistical analysis title	ITT: 5-year distant metastasis-free sur...

Statistical analysis description:

5-year distant metastasis-free survival rate was estimated by Kaplan-Meier estimate and presented with two-sided 95% CI.

Comparison groups	Phase II Intention-to-treat (ITT) v Phase II per-protocol (PP)
Number of subjects included in analysis	105
Analysis specification	Post-hoc
Analysis type	other
Parameter estimate	Rate
Point estimate	0.385
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.261
upper limit	0.507

Statistical analysis title	PP: 1-year distant metastasis-free sur...

Statistical analysis description:

1-year distant metastasis-free survival rate was estimated by Kaplan-Meier estimate and presented with two-sided 95% CI.

Comparison groups	Phase II per-protocol (PP) v Phase II Intention-to-treat (ITT)
Number of subjects included in analysis	105
Analysis specification	Post-hoc
Analysis type	other
Parameter estimate	Rate
Point estimate	0.797
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.635
upper limit	0.893

Statistical analysis title	PP: 2-year distant metastasis-free sur...
Statistical analysis description:	
2-year distant metastasis-free survival rate was estimated by Kaplan-Meier estimate and presented with two-sided 95% CI.	
Comparison groups	Phase II per-protocol (PP) v Phase II Intention-to-treat (ITT)
Number of subjects included in analysis	105
Analysis specification	Post-hoc
Analysis type	other
Parameter estimate	Rate
Point estimate	0.669
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.498
upper limit	0.792

Statistical analysis title	PP: 5-year distant metastasis-free sur...
Statistical analysis description:	
5-year distant metastasis-free survival rate was estimated by Kaplan-Meier estimate and presented with two-sided 95% CI.	
Comparison groups	Phase II per-protocol (PP) v Phase II Intention-to-treat (ITT)
Number of subjects included in analysis	105
Analysis specification	Post-hoc
Analysis type	other
Parameter estimate	Rate
Point estimate	0.443
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.279
upper limit	0.594

Secondary: Selective lymph node dissection	
End point title	Selective lymph node dissection
End point description:	
Number of subjects who had a selective lymph node dissection	
End point type	Secondary
End point timeframe:	
at end of treatment	

End point values	Phase II Intention-to-treat (ITT)	Phase II per-protocol (PP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	65	40		
Units: Subjects				
No	30	19		
Yes	16	12		
Unknown	19	9		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From date of signed informed consent until 6 weeks after the end of study treatment.

Adverse event reporting additional description:

Follow-up on any unresolved adverse events until resolved or stabilized.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups

Reporting group title	Phase I Safety analysis set

Reporting group description:

All patients in Phase I receiving at least one dose of the study treatment were evaluable for safety, 16 patients in phase I, 3/4/3/6 at dose levels 1/2/3/4

Reporting group title	Phase II Safety analysis set

Reporting group description:

All patients receiving at least one dose of the study treatment were evaluable for safety - 65 patients in phase II. Coincidentally, safety and ITT analysis sets of phase II were identical.

Serious adverse events	Phase I Safety analysis set	Phase II Safety analysis set	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 16 (37.50%)	26 / 65 (40.00%)	
number of deaths (all causes)	6	35	
number of deaths resulting from adverse events	0	2	
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 16 (6.25%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Mucosal inflammation			
subjects affected / exposed	1 / 16 (6.25%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 16 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Immune system disorders			
Hypersensitivity			
subjects affected / exposed	2 / 16 (12.50%)	3 / 65 (4.62%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 16 (6.25%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal fistula			
subjects affected / exposed	0 / 16 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 16 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pulmonary embolism			
subjects affected / exposed	0 / 16 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Alcohol withdrawal syndrome			
subjects affected / exposed	0 / 16 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Haemoglobin decreased			
subjects affected / exposed	0 / 16 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			

subjects affected / exposed	0 / 16 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoradionecrosis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 16 (0.00%)	2 / 65 (3.08%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 16 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer perforation			
subjects affected / exposed	0 / 16 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 16 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal ulceration			

subjects affected / exposed	0 / 16 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 16 (6.25%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 16 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	0 / 16 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	0 / 16 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 16 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pathological fracture			
subjects affected / exposed	0 / 16 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Abdominal infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess neck			
subjects affected / exposed	0 / 16 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 16 (0.00%)	2 / 65 (3.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia staphylococcal			
subjects affected / exposed	0 / 16 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Lactic acidosis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Phase I Safety analysis set	Phase II Safety analysis set	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 16 (100.00%)	65 / 65 (100.00%)	
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	3 / 16 (18.75%)	20 / 65 (30.77%)	
occurrences (all)	3	20	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 16 (18.75%)	12 / 65 (18.46%)	
occurrences (all)	3	12	
Blood albumin decreased			
subjects affected / exposed	1 / 16 (6.25%)	4 / 65 (6.15%)	
occurrences (all)	1	4	
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 16 (12.50%)	14 / 65 (21.54%)	
occurrences (all)	2	14	
Blood bilirubin increased			
subjects affected / exposed	2 / 16 (12.50%)	5 / 65 (7.69%)	
occurrences (all)	2	5	
Blood calcium decreased			
subjects affected / exposed	5 / 16 (31.25%)	10 / 65 (15.38%)	
occurrences (all)	5	10	
Blood creatine increased			
subjects affected / exposed	4 / 16 (25.00%)	13 / 65 (20.00%)	
occurrences (all)	4	13	
Blood magnesium decreased			
subjects affected / exposed	4 / 16 (25.00%)	7 / 65 (10.77%)	
occurrences (all)	4	7	
Blood magnesium abnormal			
subjects affected / exposed	0 / 16 (0.00%)	3 / 65 (4.62%)	
occurrences (all)	0	3	
Blood potassium decreased			
subjects affected / exposed	2 / 16 (12.50%)	3 / 65 (4.62%)	
occurrences (all)	2	3	
Blood potassium increased			
subjects affected / exposed	0 / 16 (0.00%)	3 / 65 (4.62%)	
occurrences (all)	0	3	
Blood sodium decreased			

subjects affected / exposed	1 / 16 (6.25%)	4 / 65 (6.15%)	
occurrences (all)	1	4	
C-reactive protein increased			
subjects affected / exposed	3 / 16 (18.75%)	14 / 65 (21.54%)	
occurrences (all)	3	14	
Blood urea decreased			
subjects affected / exposed	0 / 16 (0.00%)	6 / 65 (9.23%)	
occurrences (all)	0	6	
Blood uric acid increased			
subjects affected / exposed	0 / 16 (0.00%)	2 / 65 (3.08%)	
occurrences (all)	0	2	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 16 (6.25%)	11 / 65 (16.92%)	
occurrences (all)	1	11	
Haemoglobin decreased			
subjects affected / exposed	11 / 16 (68.75%)	57 / 65 (87.69%)	
occurrences (all)	11	57	
Neutrophil count decreased			
subjects affected / exposed	8 / 16 (50.00%)	18 / 65 (27.69%)	
occurrences (all)	8	18	
White blood cell count decreased			
subjects affected / exposed	11 / 16 (68.75%)	45 / 65 (69.23%)	
occurrences (all)	11	45	
Protein total decreased			
subjects affected / exposed	0 / 16 (0.00%)	3 / 65 (4.62%)	
occurrences (all)	0	3	
Injury, poisoning and procedural complications			
Platelet count decreased			
subjects affected / exposed	3 / 16 (18.75%)	22 / 65 (33.85%)	
occurrences (all)	3	22	
Radiation skin injury			
subjects affected / exposed	14 / 16 (87.50%)	60 / 65 (92.31%)	
occurrences (all)	14	60	
Vascular disorders			

Lymphoedema			
subjects affected / exposed	1 / 16 (6.25%)	3 / 65 (4.62%)	
occurrences (all)	1	3	
Hypotension			
subjects affected / exposed	0 / 16 (0.00%)	3 / 65 (4.62%)	
occurrences (all)	0	3	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	1 / 16 (6.25%)	9 / 65 (13.85%)	
occurrences (all)	1	9	
Hypotonia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 65 (1.54%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	11 / 16 (68.75%)	49 / 65 (75.38%)	
occurrences (all)	11	49	
Localised oedema			
subjects affected / exposed	1 / 16 (6.25%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Mucosal inflammation			
subjects affected / exposed	16 / 16 (100.00%)	61 / 65 (93.85%)	
occurrences (all)	16	61	
Pain			
subjects affected / exposed	14 / 16 (87.50%)	57 / 65 (87.69%)	
occurrences (all)	14	57	
Pyrexia			
subjects affected / exposed	4 / 16 (25.00%)	14 / 65 (21.54%)	
occurrences (all)	4	14	
Fibrosis			
subjects affected / exposed	0 / 16 (0.00%)	2 / 65 (3.08%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 16 (12.50%)	10 / 65 (15.38%)	
occurrences (all)	2	10	

Dry mouth			
subjects affected / exposed	15 / 16 (93.75%)	49 / 65 (75.38%)	
occurrences (all)	15	49	
Dysphagia			
subjects affected / exposed	16 / 16 (100.00%)	63 / 65 (96.92%)	
occurrences (all)	16	63	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 16 (6.25%)	1 / 65 (1.54%)	
occurrences (all)	1	1	
Oesophagitis			
subjects affected / exposed	1 / 16 (6.25%)	1 / 65 (1.54%)	
occurrences (all)	1	1	
Vomiting			
subjects affected / exposed	4 / 16 (25.00%)	18 / 65 (27.69%)	
occurrences (all)	4	18	
Constipation			
subjects affected / exposed	0 / 16 (0.00%)	7 / 65 (10.77%)	
occurrences (all)	0	7	
Dyspepsia			
subjects affected / exposed	0 / 16 (0.00%)	2 / 65 (3.08%)	
occurrences (all)	0	2	
Nausea			
subjects affected / exposed	0 / 16 (0.00%)	4 / 65 (6.15%)	
occurrences (all)	0	4	
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	11 / 16 (68.75%)	51 / 65 (78.46%)	
occurrences (all)	11	51	
Dermatitis contact			
subjects affected / exposed	1 / 16 (6.25%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Nail disorder			
subjects affected / exposed	1 / 16 (6.25%)	8 / 65 (12.31%)	
occurrences (all)	1	8	
Pruritus			

subjects affected / exposed	0 / 16 (0.00%)	2 / 65 (3.08%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Trismus			
subjects affected / exposed	0 / 16 (0.00%)	2 / 65 (3.08%)	
occurrences (all)	0	2	
Infections and infestations			
Infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Pharyngitis			
subjects affected / exposed	1 / 16 (6.25%)	2 / 65 (3.08%)	
occurrences (all)	1	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 July 2005	Change of Coordinating investigator, Change in biostatistic analysis. Approved by EC on 22.08.2005, approved by CA on 09.09.2005
04 August 2005	An association between CETUXIMAB therapy and hypomagnesaemia was reported. The majority of reported cases were dealing with asymptomatic hypomagnesaemia detected by routine electrolyte monitoring during therapy. Due to possible safety implications it was decided that patient receiving Cetuximab undergo routine monitoring of serum magnesium. Repletion of documented hypomagnesaemia had to be be carried out based on clinical judgment. Approved by EC on 22.08.2005, Approved by CA on 27.10.2005
05 April 2007	A new formulation of Erbitux® was introduced onto the market on 16th April 2007. Formulation of Erbitux® has been switched from 2mg/ml to 5mg/ml. Vials containing 20ml and 100ml Erbitux® solution were then available. It is intended to introduce The new formulation was introduced after complete consumption of Erbitux 2 mg / ml at the trial sites. Approved by EC on 23.05.2007, approved by CA on 25.04.2007.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/20427347

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