Clinical trial results:
Randomized Phase IV Trial to Compare Cetuximab with Concomitant Radiation Therapy with Concomitant Mitomycin-C and 5-FU with Radiation Therapy for Locally Advanced Squamous Cell Carcinomas of The Head and Neck

Summary

EudraCT number	2013-001296-20
Trial protocol	AT
Global end of trial date	19 April 2016

Results information

Result version number	v1 (current)
This version publication date	19 February 2017
First version publication date	19 February 2017

Trial information

Trial identification

Sponsor protocol code	MITOCET

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02015650
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medical University of Innsbruck
Sponsor organisation address	Anichstraße 35, Innsbruck, Austria, 6020
Public contact	OE Clinical Trial Center, Medical University of Innsbruck, 0043 512900370086, ctc@i-med.ac.at
Scientific contact	OE Clinical Trial Center, Medical University of Innsbruck, 0043 512900370086, ctc@i-med.ac.at

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	18 August 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 April 2016
Global end of trial reached?	Yes
Global end of trial date	19 April 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to demonstrate that Cetuximab combined with radiation therapy has a higher life quality compared to 5-FU/MMC plus radiation therapy, because of decreased side effects.

Protection of trial subjects:

Participants
- must be between ≥18 and ≤70 years of Age
- must have specific laboratory values within a certain Limit e.g. neutrophil Count ≥ 1.5 G/l
- must be medically suitable to withstand a course of definitive radiation therapy and concomitant chemotherapy or antibody-therapy
- must have a Karnofsky performance status (KPS) of ≥ 70 at the time of screening
- must not be pregnant or breastfeeding
- must not be particpating actively in another clinical trial

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 December 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 4
Worldwide total number of subjects	4
EEA total number of subjects	4

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)	0
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The recruitement of cancer patients treated at the investigational centre was referred from other institutions or from the cancer patients presented in the local head and neck tumor board review. A record of the most recent pre-treatment evaluations has been reviewed to determine the suitability of the patient for the trial.

Pre-assignment

Screening details:

Day -21/-14: Check of inclusion and exclusion criteria, performing of physical examination, vital signs and laboratory test. Verification of histology, tumor imaging and tumor assessment.

Period 1

Period 1 title	Study phase (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cetuximab

Arm description:

Cetuximab in combination with radiotherapy

Arm type	Experimental
Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	Erbitux
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

minimum of 10 weekly infusions
400 mg/m2 loading dose on week 0;
250 mg/m2 maintenance doses beginning on week 1 - 9

Arm title	Mitomycin C and 5-Flourouracil

Arm description:

Mitomycin-C and 5-Flourouracil in combination with radiotherapy

Arm type	Active comparator
Investigational medicinal product name	Mitomycin C
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

10mg/m² (max. 15 mg/d) day 8 and day 43

Investigational medicinal product name	5- Flourouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for prolonged-release suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

in total 1000 mg/m² (max. 1500mg/24h) days 8-12 and days 43–47

Number of subjects in period 1	Cetuximab	Mitomycin C and 5-Flourouracil
Started	2	2
Completed	0	0
Not completed	2	2
tumor progression	-	1
Lost to follow-up	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Cetuximab
Reporting group description: Cetuximab in combination with radiotherapy	
Reporting group title	Mitomycin C and 5-Flourouracil
Reporting group description: Mitomycin-C and 5-Flourouracil in combination with radiotherapy	

Reporting group values	Cetuximab	Mitomycin C and 5-Flourouracil	Total
Number of subjects	2	2	4
Age categorical			
In total 70 patients have been planned to be included in the trial, 35 patients for each arm.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	2	2	4
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	1	0	1
Male	1	2	3

Subject analysis sets	
Subject analysis set title	Risk and benefit analysis
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Risk of the study have been the known side effects of the products: Mitomycin-C, 5-Fluorouracil, Cetuximab and radiation therapy. These are listed in the particular
product description and the description of radiation therapy. Another risk would be that the primary objective cannot be fulfilled. So the patients would have a lower
quality of life than expected. Some of the benefits for the Patient would have been a decrease of pain medication and side effects caused by pain medication, a decrease of surgical Intervention, Improving of patients social functioning, social eating, social contact, No interruptions of therapy and Increase of life Quality.

Reporting group values	Risk and benefit analysis		
Number of subjects	4		
Age categorical			
In total 70 patients have been planned to be included in the trial, 35 patients for each arm.			
Units: Subjects			

In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over	4		
Gender categorical Units: Subjects			
Female	1		
Male	3		

End points

End points reporting groups

Reporting group title	Cetuximab
Reporting group description:	
Cetuximab in combination with radiotherapy	
Reporting group title	Mitomycin C and 5-Flourouracil
Reporting group description:	
Mitomycin-C and 5-Flourouracil in combination with radiotherapy	
Subject analysis set title	Risk and benefit analysis
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Risk of the study have been the known side effects of the products: Mitomycin-C, 5-Fluorouracil, Cetuximab and radiation therapy. These are listed in the particular product description and the description of radiation therapy. Another risk would be that the primary objective cannot be fulfilled. So the patients would have a lower quality of life than expected. Some of the benefits for the Patient would have been a decrease of pain medication and side effects caused by pain medication, a decrease of surgical Intervention, Improving of patients social functioning, social eating, social contact, No interruptions of therapy and Increase of life Quality.	

Primary: Quality of Life

End point title	Quality of Life
End point description:	
End point type	Primary
End point timeframe:	
evaluation of assessment 5 times during actice Phase and 9 times during Follow-Up	

End point values	Cetuximab	Mitomycin C and 5-Flourouracil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	2		
Units: assessment of quality of life	2	2		

Statistical analyses

Statistical analysis title	Statistics primary endpoint active phase
Comparison groups	Cetuximab v Mitomycin C and 5-Flourouracil
Number of subjects included in analysis	4
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.05 [2]
Method	Fisher exact

Notes:

[1] - The primary objective of this study is to compare whether a combination therapy with Cetuximab improves
patient`s quality of life measured with EORTC QLQ-C30 plus H&N35.
The primary objective of this study is to compare whether a combination therapy with Cetuximab reduces
toxicity regarding the occurrence of rash and mucositis.

[2] - The primary analysis population will comprise all randomized patients according to the intention-to-treat
principle; a secondary per-protocol analysis will exclude patients with major protocol deviations. Statistical
tests will generally be two-sid

Secondary: Response rate

End point title	Response rate

End point description:

End point type	Secondary

End point timeframe:

No assessment during active Phase, 4 times assessment during Follow-Up phase

Statistical analyses

No statistical analyses for this end point

Secondary: Differences in locoregional disease control

End point title	Differences in locoregional disease control

End point description:

End point type	Secondary

End point timeframe:

No assessment during active Phase, 4 times assessment during Follow-Up.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From patient inclusion to drop-out respectively permature termination of the study

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	Cetuximab

Reporting group description:

Cetuximab in combination with radiotherapy

Reporting group title	Mitomycin C and 5-Flourouracil

Reporting group description:

Mitomycin-C and 5-Flourouracil in combination with radiotherapy

Serious adverse events	Cetuximab	Mitomycin C and 5-Flourouracil	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)	1 / 2 (50.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Brachial plexopathy			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Reduced appetite	Additional description: Reduced general condition due to reduced appetite caused by combinated radioimmunotherapy.		
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia and thrombocytopenia	Additional description: Recently diagnosed pancreatic cancer with livermetastases. Patinet recieved chemotherapy with cisplatin. Leucopenia, neutropenia and thrombopenia are caused by chemotherapy.		
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Dysphagia	Additional description: Expected side effects like dyphagia and increase mucus production seem straining for the patient so that the patient couldn't continue therapy in an ambulant setting.		
subjects affected / exposed	0 / 2 (0.00%)	1 / 2 (50.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Tracheal stenosis and laryngeal dyspnoea			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cetuximab	Mitomycin C and 5-Flourouracil	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)	2 / 2 (100.00%)	
General disorders and administration site conditions			
Fatigue	Additional description: Grade 1		
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Edema face	Additional description: Grade 1		
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Laryngeal mucositis	Additional description: Grade 1, 2		
subjects affected / exposed	2 / 2 (100.00%)	1 / 2 (50.00%)	
occurrences (all)	6	1	
Sore throat	Additional description: Grade 1		
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Productive cough	Additional description: Grade 1		
subjects affected / exposed	0 / 2 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	1	
Hoarseness	Additional description: Grade 1, 2		

subjects affected / exposed	0 / 2 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	2	
Laryngeal stenosis	Additional description: Grade 1		
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Anorexia	Additional description: Grade 1, 2		
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Insomnia	Additional description: Grade 1		
subjects affected / exposed	2 / 2 (100.00%)	0 / 2 (0.00%)	
occurrences (all)	3	0	
Injury, poisoning and procedural complications			
Dermatitis radiation	Additional description: Grade 1, 2		
subjects affected / exposed	2 / 2 (100.00%)	0 / 2 (0.00%)	
occurrences (all)	3	0	
Nervous system disorders			
Dysgeusia	Additional description: Grade1, 2		
subjects affected / exposed	2 / 2 (100.00%)	1 / 2 (50.00%)	
occurrences (all)	2	1	
Lethargy	Additional description: Grade 1		
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Leukocytosis	Additional description: Grade 1		
subjects affected / exposed	0 / 2 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Vertigo	Additional description: Grade 1		
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Dysphagia	Additional description: Grade 1, 2, 3		
subjects affected / exposed	2 / 2 (100.00%)	2 / 2 (100.00%)	
occurrences (all)	3	4	
Dry mouth	Additional description: Grades 1, 2, 3		

subjects affected / exposed	2 / 2 (100.00%)	1 / 2 (50.00%)	
occurrences (all)	4	1	
Vomiting	Additional description: Grade 1		
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Constipation	Additional description: Grade 3		
subjects affected / exposed	2 / 2 (100.00%)	0 / 2 (0.00%)	
occurrences (all)	3	0	
Gastritis	Additional description: Grade 1		
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Mucositis oral	Additional description: Grade 1, 2		
subjects affected / exposed	0 / 2 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	4	
Stomach pain	Additional description: Grade 1		
subjects affected / exposed	0 / 2 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	1	
Gastroesophageal reflux disease	Additional description: Grade 1		
subjects affected / exposed	0 / 2 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Rash acneiform	Additional description: rash face and/or rash body; Grade 1, two and/or 3		
subjects affected / exposed	2 / 2 (100.00%)	0 / 2 (0.00%)	
occurrences (all)	4	0	
Erythema PEG placing	Additional description: Grade 1		
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Dermatitis	Additional description: Grade 1		
subjects affected / exposed	0 / 2 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	1	
Endocrine disorders			
Hyperthyroidism	Additional description: latent hyperthyreodism, Grade 1		
subjects affected / exposed	2 / 2 (100.00%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Hypothyroidism	Additional description: Grade 1		

subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Hyperthyroidism with isolated FT4 increase	Additional description: Grade 1		
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia	Additional description: Grade 1		
subjects affected / exposed	0 / 2 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	2	
Infections and infestations			
Paronychia	Additional description: Grade 1		
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection	Additional description: Grade 1		
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hypophosphatemia	Additional description: Grade 1		
subjects affected / exposed	2 / 2 (100.00%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Hypomagnesemia	Additional description: Grade 1		
subjects affected / exposed	0 / 2 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	1	
Hyperuricemia	Additional description: Grade 1		
subjects affected / exposed	0 / 2 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	1	
Hyperglycemia	Additional description: Grade 2		
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Hypoalbuminemia	Additional description: Grade 1		
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 February 2015	Change of inclusion criteria in order to fullfill the recruitment rate

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

low recruitment rate

Notes: