Clinical trial results:
Do Selective Radiation Dose Escalation and Tumor Hypoxia Status Impact the Locoregional Tumor Control after Radiochemotherapy of Head & Neck Tumors?

Summary

EudraCT number	2010-021139-15
Trial protocol	DE
Global end of trial date	18 December 2017

Results information

Result version number	v1 (current)
This version publication date	08 November 2020
First version publication date	08 November 2020

Trial information

Trial identification

Sponsor protocol code	ESC-928-MOL-0000-I

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Technische Universität München, Fakultät für Medizin
Sponsor organisation address	Ismaninger Str. 22, München, Germany, 81675
Public contact	Dr. med. Steffi Pigorsch, Klinikum rechts der Isar der TU München, Klinik und Poliklinik für RadioOnkologie und Strahlentherap, 0049 8941404501, steffi.pigorsch@mri.tum.de
Scientific contact	Dr. med. Steffi Pigorsch, Klinikum rechts der Isar der TU München, Klinik und Poliklinik für RadioOnkologie und Strahlentherap, 0049 8941404501, steffi.pigorsch@mri.tum.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	04 March 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 October 2017
Global end of trial reached?	Yes
Global end of trial date	18 December 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Following the requirements of the Bundesamt für Strahlenschutz the primary objective of the pre-study is to assess the occurence of radiogenic toxicities.
The main Escalox-trial hypothesizes an improvement in the 2-year loco-regional tumor control and survival in patients of explorative trial arm A in comparison to patients of arm B which undergo standard radiotherapy due to the use of Radiation dose escalation to a sub-volume of the gross tumor volume of locally advanced head and neck cancer in arm A. Primary objective: Does a selective radiation dose escalation to gross Tumor volume improve loco-regional control and survival over 2 years?

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance the ethical principles of Good Clinical Practice (GCP).
Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision.
The study was regularly monitored by the Sponsor and all investigators connected to the study were GCP trained. The study was approved by the Federal Office for Radiation Protection (BfS) following an application by the sponsor.

Background therapy:

The chemotherapy treatment of the Escalox trial will use cisplatin in the 1st and 5th week of the radiotherapy given on 5 days with an absolute dose of 200mg/m².

Evidence for comparator:

n.a.

Actual start date of recruitment	17 January 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 6
Worldwide total number of subjects	6
EEA total number of subjects	6

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)	3
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Pre-screening processes were in place for all patients. 6 patients were randomised between 17.01.2016 and 10.10.2017. For safety aspects the permisson of the Bfs demanded a pre-study with a 1st step dose-escalation of 2.2 Gy to 77.0 Gy to the GTV with 20 additional patients.

Pre-assignment

Screening details:

After the QA-RT approval, patients must have all screening evaluations performed prior to the first dose and must meet all inclusion and none of the exclusion criteria. The patients must be thoroughly informed about all aspects of the study. The first patient was screened in 12/2015; on January 2017 he was enrolled.

Period 1

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

Arms

Arm title	Step one

Arm description:

Step one in a stepwise sewiential design

Arm type	Experimental
Investigational medicinal product name	18F-FMISO
Investigational medicinal product code	
Other name	MISONIDAZOLE (INN); SUB08997MIG (CAS number); 18-F-MFISO: Fluoromisonidazol - tracer to detect hypoxic cells
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Total 740 MBq megabecquerel(s)

Number of subjects in period 1	Step one
Started	6
Completed	0
Not completed	6
premature study termination	6

Baseline characteristics

Reporting groups

Reporting group title	per-study stage

Reporting group description: -

Reporting group values	per-study stage	Total	
Number of subjects	6	6	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
median	61		
full range (min-max)	53 to 70	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	6	6	

Subject analysis sets

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

Includes all patients who entered the study.

Reporting group values	Full analysis set		
Number of subjects	6		
Age categorical 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			

Age continuous Units: years median full range (min-max)	 61 53 to 70		
Gender categorical Units: Subjects			
Female Male	0 6		

End points

End points reporting groups

Reporting group title	Step one
Reporting group description: Step one in a stepwise sewiential design	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description: Includes all patients who entered the study.	

Primary: Radiation-induced toxicity

End point title	Radiation-induced toxicity[1]
End point description:	
End point type	Primary
End point timeframe: throughout the study	

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: No statistical testing was planned for the pre-study.

End point values	Step one			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Patients				
yes	6			
no	0			

Statistical analyses

No statistical analyses for this end point

Primary: Mean number of radiation-indiced toxicities per patient

End point title	Mean number of radiation-indiced toxicities per patient[2]
End point description:	
End point type	Primary
End point timeframe: Throughout the study.	

Notes:

[2] - 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: No statistical testing was planned for the pre-study.

End point values	Step one			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: number of toxicities				
number (not applicable)	12.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean weight loss

End point title	Mean weight loss

End point description:

End point type	Secondary

End point timeframe:
throughout the study

End point values	Step one			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: percent weight/weight				
arithmetic mean (standard deviation)	9.0 (± 2.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum weight loss

End point title	Maximum weight loss

End point description:

End point type	Secondary

End point timeframe:
throughout the study

End point values	Step one			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: percent weight/weight				
arithmetic mean (standard deviation)	15.8 (± 5.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean number of late side effects of grade 3

End point title	Mean number of late side effects of grade 3

End point description:

End point type	Secondary

End point timeframe:

LENT/SOMA late toxicities

End point values	Step one			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: number				
number (not applicable)	2.8			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE Assessment is performed every week during treatment and start of follow-up including acute toxicities according to CTCAE v.4.0. For longterm follow up only late toxicities (according to LENT-SOMA) are assessed.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	All patients

Reporting group description:

All patients who entered the study.

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to lymph nodes			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Non-small cell lung cancer metastatic			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Injury, poisoning and procedural complications			
Gastrointestinal stoma complication			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Radiation mucositis			

subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Stoma closure			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Mucosal pain			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Mucosal ulceration			
subjects affected / exposed	3 / 6 (50.00%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis			

subjects affected / exposed	1 / 6 (16.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea haemorrhagic				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestinal haemorrhage				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mouth ulceration				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Stomatitis				
subjects affected / exposed	4 / 6 (66.67%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Dyspnoea				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Tracheal stenosis				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				

Skin oedema			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Oral infection			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Superinfection			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 6 (16.67%)		
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	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Gastrointestinal tract adenoma subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Vascular disorders Hypertension subjects affected / exposed occurrences (all) Thrombophlebitis superficial subjects affected / exposed occurrences (all)	 1 / 6 (16.67%) 1 1 / 6 (16.67%) 1		
General disorders and administration site conditions Localised oedema subjects affected / exposed occurrences (all) Mucosal inflammation subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	 3 / 6 (50.00%) 3 2 / 6 (33.33%) 2 1 / 6 (16.67%) 1 2 / 6 (33.33%) 2 1 / 6 (16.67%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Pharyngeal oedema subjects affected / exposed occurrences (all)	 1 / 6 (16.67%) 1 1 / 6 (16.67%) 1 1 / 6 (16.67%) 1		

Investigations			
Blood creatine increased			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	3		
C-reactive protein increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	6 / 6 (100.00%)		
occurrences (all)	6		
Injury, poisoning and procedural complications			
Gastrointestinal stoma complication			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Radiation mucositis			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Radiation skin injury			
subjects affected / exposed	5 / 6 (83.33%)		
occurrences (all)	5		
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	5 / 6 (83.33%)		
occurrences (all)	7		
Peripheral nerve lesion			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 6 (66.67%)		
occurrences (all)	7		
Febrile neutropenia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Leukocytosis			

subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Leukopenia			
subjects affected / exposed	6 / 6 (100.00%)		
occurrences (all)	6		
Thrombocytopenia			
subjects affected / exposed	4 / 6 (66.67%)		
occurrences (all)	4		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	3 / 6 (50.00%)		
occurrences (all)	3		
Dry mouth			
subjects affected / exposed	6 / 6 (100.00%)		
occurrences (all)	6		
Dysphagia			
subjects affected / exposed	6 / 6 (100.00%)		
occurrences (all)	7		
Flatulence			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Haematochezia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Mouth ulceration			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Oral dysaesthesia			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	2		
Anal haemorrhage			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		

Odynophagia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Oral pain			
subjects affected / exposed	3 / 6 (50.00%)		
occurrences (all)	3		
Vomiting			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Infections and infestations			
Device related infection			
subjects affected / exposed	3 / 6 (50.00%)		
occurrences (all)	6		
Herpes zoster			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Mucosal infection			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	2		
Oral candidiasis			
subjects affected / exposed	3 / 6 (50.00%)		
occurrences (all)	4		

Pneumonia			
subjects affected / exposed	3 / 6 (50.00%)		
occurrences (all)	3		
Skin infection			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Staphylococcal infection			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Superinfection bacterial			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Superinfection fungal			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Hypoalbuminaemia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Hypocalcaemia			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	2		
Hypokalaemia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Hyponatraemia			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	2		
Malnutrition			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
23 August 2017	Recruitment was stopped (advice SMB): 23.08.2017 before the clinical trial was terminated early (at pre-study stage) by the LKP: 18.12.2017 Because of appearance of early Late-toxicities: 4 out of 6 patients developed extended local mucositis with ulcerations in the initial tumor bed due to radiation dose escalation, trial was interrupted.	-

Notes:

Limitations and caveats

None reported