Clinical trial results:
Metabolic Response Evaluation for an Individualization of Neoadjuvant Chemo- and Radiotherapy in Esophageal Adenocarcinoma

Summary

EudraCT number	2005-004123-19
Trial protocol	DE
Global end of trial date	17 April 2014

Results information

Result version number	v1 (current)
This version publication date	17 July 2020
First version publication date	17 July 2020
Summary attachment (see zip file)	MUNICON II Trial (MUNICON_II_2011.pdf)

Trial information

Trial identification

Sponsor protocol code	MUNICON-2

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	Klinik und Poliklinik für Innere Medizin II Studiensekretariat Jens-Peter Zimmermann , Technische Universität München, Fakultät für Medizin, 49 89 4140 6706,
Scientific contact	Klinikum rechts der Isar Klinik und Poliklinik für Innere Medizin II, Technische Universität München, Fakultät für Medizin, 49 89 4140 2250,

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	25 March 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 April 2014
Global end of trial reached?	Yes
Global end of trial date	17 April 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The aim of this prospective trial is to optimize current treatment for patient with chemoresistant locally advanced adenocarcinomas of the esophagogastric junction (AEG Typ I und II).
Compared to the previous protocol MUNICON-1, introduction of a new treatment regimen with using a salvage neoadjuvant radiochemotherapy.

The intention is to investigate in case of metabolic non-Response under neoadjuvant chemotherapie the effectiveness of a radiochemotherapy based on the metabolic Response (primary endpoint) and histological regression (secondary endpoint). In addition, the tolerability of preoperative radiochemotherapy, the rate of residual tumour-free resections as well as overall survival and event-free survival will also be assessed.

Protection of trial subjects:

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.

Background therapy:

Concomitant medication and supportive therapy were carried out according to standard clinical guidelines and at the judgement of the investigators.

Evidence for comparator:

Previous studies demonstrated that chemotherapy-induced changes in tumor glucose metabolism measured with 18F-FDG PET identify patients who benefit from preoperative chemotherapy and those who do not. The prognosis for chemotherapy metabolic nonresponders is poorer than for metabolic responders. (MUNICON I).

Group B = 1:1
Group A, Control Group (18FDG-PET (PET)-Responder: neoadjuvante Chemotherapie
Group B, Treatmeant Group (PET-Non-Responder: neoadjuvante Radiochemotherapie)

Actual start date of recruitment	28 September 2005
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	60 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 56
Worldwide total number of subjects	56
EEA total number of subjects	56

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)	46
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted single-centre in Germany between 28.09.2005 (first patient recruited) and 17.04.2014 (last patient completed).

Pre-assignment

Screening details:

Patients were enrolled to the study, if eligibility was confirmed. A total of 66 patients were screened, 56 were included in the study.
According to Gehan's two-stage design, the number of planned cases for this study was 25 patients in test arm B (PET non-responder; neoadjuvant radiochemotherapy).

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	A: Control Group - PET Responder

Arm description:

18F-FDG PET assessement before chemotherapy and 14 d after initiation of chemotherapy. PET responder (metabolic response) receive neoadjuvant chemotherapy for 3 mo before surgery

Group A: Control Group (PET-Responder; neoadjuvante Chemotherapie)

Arm type	Active comparator
Investigational medicinal product name	PACLITAXEL
Investigational medicinal product code	SUB09583MIG
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Total: 85 mg/m2 milligram(s)/square meter

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	L01XA01
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Total: 50 mg/m2 milligram(s)/square meter

Investigational medicinal product name	Calciumfolinat
Investigational medicinal product code	L01BA01
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Total: 500 mg/m2 milligram(s)/square meter

Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	L01BC02
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Total: 2000 mg/m2 milligram(s)/square meter

Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	L01XA03
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Total: 85 mg/m2 milligram(s)/square meter

Arm title	B. Treatment Group - Non-Responder

Arm description:

18F-FDG PET assessement before chemotherapy and 14 d after initiation of chemotherapy. PET non-responder receive salvage neoadjuvant radiochemotherapy (2 x 1,6 Gy/d, total dose 32 Gy) before surgery

Group B: Treatment Group (PET-Non-Responder; neoadjuvante Radiochemotherapie)

Arm type	Experimental
Investigational medicinal product name	CISPLATIN
Investigational medicinal product code	L01XA01
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Total: 50 mg/m2 milligram(s)/square meter

Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	L01BC02
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Total: 2000 mg/m2 milligram(s)/square meter

Number of subjects in period 1	A: Control Group - PET Responder	B. Treatment Group - Non-Responder
Started	33	23
Completed	33	23

Baseline characteristics

Reporting groups

Reporting group title	A: Control Group - PET Responder

Reporting group description:

18F-FDG PET assessement before chemotherapy and 14 d after initiation of chemotherapy. PET responder (metabolic response) receive neoadjuvant chemotherapy for 3 mo before surgery

Group A: Control Group (PET-Responder; neoadjuvante Chemotherapie)

Reporting group title	B. Treatment Group - Non-Responder

Reporting group description:

18F-FDG PET assessement before chemotherapy and 14 d after initiation of chemotherapy. PET non-responder receive salvage neoadjuvant radiochemotherapy (2 x 1,6 Gy/d, total dose 32 Gy) before surgery

Group B: Treatment Group (PET-Non-Responder; neoadjuvante Radiochemotherapie)

Reporting group values	A: Control Group - PET Responder	B. Treatment Group - Non-Responder	Total
Number of subjects	33	23	56
Age categorical Units: Subjects			
Age continuous Units: years			
median	60	65	
inter-quartile range (Q1-Q3)	35 to 75	36 to 72	-
Gender categorical Units: Subjects			
Male	30	21	51
Female	3	2	5
AEG Units: Subjects			
Type I	21	18	39
Type II	12	5	17

End points

End points reporting groups

Reporting group title	A: Control Group - PET Responder

Reporting group description:

18F-FDG PET assessement before chemotherapy and 14 d after initiation of chemotherapy. PET responder (metabolic response) receive neoadjuvant chemotherapy for 3 mo before surgery

Group A: Control Group (PET-Responder; neoadjuvante Chemotherapie)

Reporting group title	B. Treatment Group - Non-Responder

Reporting group description:

18F-FDG PET assessement before chemotherapy and 14 d after initiation of chemotherapy. PET non-responder receive salvage neoadjuvant radiochemotherapy (2 x 1,6 Gy/d, total dose 32 Gy) before surgery

Group B: Treatment Group (PET-Non-Responder; neoadjuvante Radiochemotherapie)

Primary: R0 resection

End point title	R0 resection

End point description:

End point type	Primary

End point timeframe:

Assessed after surgery

End point values	A: Control Group - PET Responder	B. Treatment Group - Non-Responder		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	23		
Units: Patients				
R0 resection	27	16		
R1 resection	2	3		
Unknown	4	4		

Statistical analyses

Statistical analysis title	R0 resection rate of non-responders

Statistical analysis description:

This is the primary endpoint of the study. The R0 resection rate was assessed according to protocol in the group of non-responders and was compared to 30%. The primary endpoint of this study was not achieved.

Comparison groups	A: Control Group - PET Responder v B. Treatment Group - Non-Responder

Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	frequency
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.84

Secondary: Metabolic Response

End point title	Metabolic Response

End point description:

Metabolic response is defined as reduction of at least 30% in maxSUV-value as compared to start of radiotherapy.

End point type	Secondary

End point timeframe:

Assessed 14 days after start of the neoadjuvant Radiochemotherapy.

End point values	A: Control Group - PET Responder	B. Treatment Group - Non-Responder		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	23		
Units: Percentage	27	16		

Statistical analyses

No statistical analyses for this end point

Secondary: Histological Remission

End point title	Histological Remission

End point description:

End point type	Secondary

End point timeframe:

At end of therapy

End point values	A: Control Group - PET Responder	B. Treatment Group - Non-Responder		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	23		
Units: patients				
I-a	4	1		
I-b	8	5		
II	7	7		
III	13	9		
Unknown	1	1		

Statistical analyses

Statistical analysis title	Histopathological remission rate
Statistical analysis description: According to the study protocol, only the group of PER-responders was used for this analysis.	
Comparison groups	B. Treatment Group - Non-Responder v A: Control Group - PET Responder
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	frequency
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	0.28

Secondary: Overall survival

End point title	Overall survival
End point description: Patients who died during the trial	
End point type	Secondary
End point timeframe: Starting at first dose of chemotherapy.	

End point values	A: Control Group - PET Responder	B. Treatment Group - Non-Responder		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	23		
Units: Patients	12	13		

Statistical analyses

Statistical analysis title	Overall Survival
Statistical analysis description: Hazard ratio	
Comparison groups	A: Control Group - PET Responder v B. Treatment Group - Non-Responder
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	4.24

Secondary: Progression-free survival	
End point title	Progression-free survival
End point description:	
End point type	Secondary
End point timeframe: Starting with first dose of Chemotherapy	

End point values	A: Control Group - PET Responder	B. Treatment Group - Non-Responder		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	23		
Units: Patients	13	15		

Statistical analyses

Statistical analysis title	Progression-free survival
Statistical analysis description: Time to relapse	
Comparison groups	A: Control Group - PET Responder v B. Treatment Group - Non-Responder
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.035
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	2.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.04
upper limit	4.77

Secondary: Postoperative morbidity	
End point title	Postoperative morbidity
End point description:	
End point type	Secondary
End point timeframe: Starting with surgery and ending with end of study	

End point values	A: Control Group - PET Responder	B. Treatment Group - Non-Responder		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	23		
Units: Patients				
Toxizität	20	16		

Statistical analyses

Statistical analysis title	Difference in post-OP morbidity
Comparison groups	A: Control Group - PET Responder v B. Treatment Group - Non-Responder

Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.68
Method	Chi-squared

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE (SAE) reporting covers the time frame from January 24th, 2006 to January 23th, 2011.

Adverse event reporting additional description:

A total of 407 AEs were reported during the study, whereby all patients reported AEs at one or more points in time during chemo- or radiochemotherapy.
In total, 234 AEs occurred after the first cycle (167 CTCAE G1, 46 CTCAE G2 and 20 CTCAE G3 and 1 CTCAE G4).
Each adverse event is to be classified by the investigator as SERIOUS or NON-SERIOUS.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14

Reporting groups

Reporting group title	All patients

Reporting group description:

As expected, the PET responders, who received an extended cycle 1 and a cycle 2 of chemotherapy, reported significantly more AEs than the PET non-responders, who discontinued chemotherapy after a 2-week cycle 1 and continued treatment with chemoradiation.

A total of 407 AEs occurred in 56 patients.
The PET responders had 170 AEs (111 CTCAE G1, 41 CTCAE G2 and 17 CTCAE G3 and 1 CTCAE G4) after cycle 1 and 114 AEs (79 CTCAE G1, 32 CTCAE G2 and 1 CTCAE G3 and 2 CTCAE G4) after cycle 2 Chemotherapy.
The PET non-responders had 64 AEs (56 CTCAE G1, 5 CTCAE G2 and 3 CTCAE G3) after cycle 1 and 59 AEs (41 CTCAE G1, 11 CTCAE G2 and 7 CTCAE G3) after chemoradiation.

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 56 (23.21%)		
number of deaths (all causes)	35		
number of deaths resulting from adverse events	1		
Injury, poisoning and procedural complications			
Anastomotic stenosis	Additional description: The subject who was affected with this SAE, belong to the group Responder.		
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 35		
Surgical and medical procedures			
Anastomotic leak	Additional description: Death in post-opearative hospitalization with intrathoracic anastomosis; septal course with terminal cardiovascular failure. One subject who was affected with this SAE, belong to the Non-Responder, two subjects belongs to the Responder Group.		

subjects affected / exposed	3 / 56 (5.36%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	1 / 35		
Blood and lymphatic system disorders			
Febrile neutropenia	Additional description: The subject who was affected with this SAE, belongs to the group Responder.		
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 35		
Gastrointestinal disorders			
Diarrhoea	Additional description: All subjects who were affected with this SAE belongs to the group Responder.		
subjects affected / exposed	3 / 56 (5.36%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 35		
Stomatitis and Ösophatitis due to herpes simplex	Additional description: The subject who was affected with this SAE, belong to the group Responder.		
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 35		
Respiratory, thoracic and mediastinal disorders			
Pleural disorder	Additional description: protracted post-op Progress The subject who was affected with this SAE, belong to the group Responder.		
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 35		
Infections and infestations			
Infection	Additional description: One subject were affected with fever with inflammation of the PEG injection port. One subject were affected with infection of unknown genesis. The subjects who were affected with this SAEs, belongs to the group Responder.		
subjects affected / exposed	2 / 56 (3.57%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 35		
Pneumonia	Additional description: The subject was affected with fever, pneumonia, Nausea and vomiting. The subject who was affected with this SAE, belong to the group Responder.		
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 35		

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

Non-serious adverse events	All patients		
Total subjects affected by non-serious adverse events subjects affected / exposed	56 / 56 (100.00%)		
Investigations			
Haemoglobin			
subjects affected / exposed	48 / 56 (85.71%)		
occurrences (all)	78		
White blood cell count			
subjects affected / exposed	22 / 56 (39.29%)		
occurrences (all)	29		
Neutrophil count			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	4		
Thrombocyte count			
subjects affected / exposed	18 / 56 (32.14%)		
occurrences (all)	22		
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	6 / 56 (10.71%)		
occurrences (all)	11		
Dizziness			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
Dysgeusia			
subjects affected / exposed	8 / 56 (14.29%)		
occurrences (all)	11		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	28 / 56 (50.00%)		
occurrences (all)	41		
Pyrexia			

subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 3 3 / 56 (5.36%) 4		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dysphagia subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Stomatitis subjects affected / exposed occurrences (all)	 24 / 56 (42.86%) 29 10 / 56 (17.86%) 11 18 / 56 (32.14%) 19 21 / 56 (37.50%) 25 15 / 56 (26.79%) 18 7 / 56 (12.50%) 7		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	 6 / 56 (10.71%) 11		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 12 / 56 (21.43%) 13		

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? No

Limitations and caveats

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

Despite two recruitment extensions, the number of cases could not be reached.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/24817185

http://www.ncbi.nlm.nih.gov/pubmed/21764790

http://www.ncbi.nlm.nih.gov/pubmed/17693134