Clinical trial results:
Metabolic and Molecular Response Evaluation for the Individualization of Therapy in Adenocarcinomas of the Gastroesophageal Junction (MeMoRI)

Summary

EudraCT number	2014-000860-16
Trial protocol	DE
Global end of trial date	07 August 2020

Results information

Result version number	v1 (current)
This version publication date	25 August 2021
First version publication date	25 August 2021
Summary attachment (see zip file)	CSR_MeMoRI (Ergebnisbericht_MEMORI_2021_08_06_final.pdf)

Trial information

Trial identification

Sponsor protocol code	MEM-0000-SIV-0028-I

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02287129
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Technische Universität München
Sponsor organisation address	Ismaninger Str. 22, Munich, Germany, 81675
Public contact	Prof. Dr. med. Jens Siveke, Universitätsklinikum Essen, Westdeutsches Tumorzentrum, Innere Klinik, 0049 2017233704, Jens.Siveke@uk-essen.de
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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 August 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 August 2020
Global end of trial reached?	Yes
Global end of trial date	07 August 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Neoadjuvant therapy optimization in metabolic PET-Non-responders (P-NR) for improved R0 resection rates in locally advanced AEG

(R0 resection rate of patients suffering from metabolically (following PET criteria) chemotherapy-resistant, locally advanced AEG, who receive a more intensive neoadjuvant radio-chemotherapy (INRCT))

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.

Background therapy:

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

Evidence for comparator:

n.a.

Actual start date of recruitment	05 December 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 75
Worldwide total number of subjects	75
EEA total number of subjects	75

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)	49
From 65 to 84 years	26
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted multicentric in Germany between 05.12.2014 (first Patient recruited) and 07.08.2020 (last patient completed).

Pre-assignment

Screening details:

Pre-screening processes were in place.
The measures for tumor staging and for testing of functional operability follwos the standard Guidelines of the test centers.
The Screening should take place 14 days before inclusion in the study.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This is a single arm, open label study

Arms

Arm title	All patients

Arm description:

single arm, therapeutic explorative phase II clinical multi-center trial

Arm type	All patients
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	ATC L01CD02; Substance Code SUB09583MIG
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Per day: 50 mg/m2 milligram(s)/square meter

Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	ATC-Code L01XA03, EV Substance code SUB09490MIG
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Per day: 130 mg/m2 milligram(s)/square meter

Investigational medicinal product name	Epirubicinhydrochlorid
Investigational medicinal product code	ATC Code: L01 DB03
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Per day: 50 mg/m2 milligram(s)/square meter

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	ATC Code: L01XA02, SUB06614MIG
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: Per day: 2 mg/ml milligram(s)/millilitre	
Investigational medicinal product name	Capecitabin
Investigational medicinal product code	ATC Code: L01BC06
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Per day: 1250 mg/m2 milligram(s)/square meter	
Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	ATC Code: L01BC02
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: Per day: 200 mg/m2 milligram(s)/square meter	
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	ATC Code: L01XA01
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: Per day: 80 mg/m2 milligram(s)/square meter	
Investigational medicinal product name	Folinsäure,
Investigational medicinal product code	ATC Code: V03AF03
Other name	Folinic acid
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: Per day: 200 mg/m2 milligram(s)/square meter	

Number of subjects in period 1	All patients
Started	75
Completed	33
Not completed	42
Adverse event, serious fatal	14
Consent withdrawn by subject	5
Diverse	13
Lost to follow-up	9
Protocol deviation	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	75	75	
Age categorical Units: Subjects			
Adults (18-64 years)	49	49	
From 65-84 years	26	26	
Gender categorical Units: Subjects			
Female	9	9	
Male	66	66	
Responder classification			
Patients are classified in responders (P-R) and non-responders (P-NR) according to RET assessment.			
Units: Subjects			
P-R	50	50	
R-NR	25	25	
Tumor size Units: Subjects			
Tx	2	2	
T2	8	8	
T3	62	62	
T4	3	3	
Lymph nodes involved Units: Subjects			
Nx	48	48	
N0	7	7	
N1	17	17	
N2	3	3	
Distant metastases Units: Subjects			
M0	74	74	
M1	1	1	
Grading Units: Subjects			
G1	6	6	
G2	32	32	
G3	33	33	
Unknown	4	4	

Subject analysis sets

Subject analysis set title	Responder
Subject analysis set type	Full analysis

Subject analysis set description:
PET responder

Subject analysis set title	Non-responder
Subject analysis set type	Full analysis

Subject analysis set description:
PET non-responder

Reporting group values	Responder	Non-responder	
Number of subjects	50	25	
Age categorical Units: Subjects			
Adults (18-64 years)	34	15	
From 65-84 years	16	10	
Gender categorical Units: Subjects			
Female	6	3	
Male	44	22	
Responder classification			
Patients are classified in responders (P-R) and non-responders (P-NR) according to RET assessment.			
Units: Subjects			
P-R	50	0	
R-NR	0	25	
Tumor size Units: Subjects			
Tx	1	1	
T2	4	4	
T3	42	20	
T4	3	0	
Lymph nodes involved Units: Subjects			
Nx	34	14	
N0	4	3	
N1	11	6	
N2	1	2	
Distant metastases Units: Subjects			
M0	49	25	
M1	1	0	
Grading Units: Subjects			
G1	4	2	
G2	24	8	
G3	21	12	
Unknown	1	3	

End points

End points reporting groups

Reporting group title	All patients
Reporting group description: single arm, therapeutic explorative phase II clinical multi-center trial	
Subject analysis set title	Responder
Subject analysis set type	Full analysis
Subject analysis set description: PET responder	
Subject analysis set title	Non-responder
Subject analysis set type	Full analysis
Subject analysis set description: PET non-responder	

Primary: R0 in P-NR

End point title	R0 in P-NR
End point description: R0 resection rate in PET non-responders that were treated according to the study protocol	
End point type	Primary
End point timeframe: Measured after surgery	

End point values	All patients	Non-responder		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	22[1]	22[2]		
Units: Subjects				
R0	19	19		
other	3	3		

Notes:

[1] - The per-protocol set of P-NR consisted of 22 patients.

[2] - The per-protocol set of P-NR consisted of 22 patients.

Statistical analyses

Statistical analysis title	Compare R0 to 0.70
Statistical analysis description: Compare the R0 resection rate on the set of per-protocol treated P-NR patients to the pre-defined value of 0.70 using the one-sided exact binomial test.	
Comparison groups	All patients v Non-responder
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.068 [4]
Method	Exact binomial test
Parameter estimate	rate
Point estimate	86.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	65.1
upper limit	97.1

Notes:

[3] - Due to limitations of the EUDRACT database, it is not possible to enter comparative statistics using one study arm and a fixed value. This is why the patient number appears double. Only 22 patients were used to evaluate the primary endpoint.

[4] - One-sided

Secondary: Histological regression

End point title	Histological regression

End point description:

Histological grade defined by Becker Criteria measured on the per-protocol set

End point type	Secondary

End point timeframe:

Measured between day 28 and 43 after radio-chemotherapy.

End point values	All patients	Responder	Non-responder	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	67[5]	45[6]	22[7]	
Units: Subjects				
Grade 1	26	14	12	
Grade 2	24	18	6	
Grade 3	17	13	4	

Notes:

[5] - The per-protocol set consisted of 67 patients.

[6] - The per-protocol set of P-R consisted of 45 patients.

[7] - The per-protocol set of P-NR consisted of 22 patients.

Statistical analyses

No statistical analyses for this end point

Secondary: Overal survival

End point title	Overal survival

End point description:

Kaplan-Meier estimates for the overal survival.

End point type	Secondary

End point timeframe:

24 months

End point values	All patients	Responder	Non-responder	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	67[8]	45[9]	22[10]	
Units: months				
arithmetic mean (confidence interval 95%)	80.3 (67.1 to 88.6)	86.9 (71.2 to 94.4)	66.2 (39.6 to 83.3)	

Notes:

[8] - The per-protocol set consisted of 67 patients.

[9] - The per-protocol set of P-R consisted of 45 patients.

[10] - The per-protocol set of P-NR consisted of 22 patients.

Statistical analyses

No statistical analyses for this end point

Secondary: Disease-free survival

End point title	Disease-free survival

End point description:

Kaplan-Meier estimate of the disease-free survival, defined as the period from start of study to earlier occuring event: death or relapse.

End point type	Secondary

End point timeframe:

24 months

End point values	All patients	Responder	Non-responder	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	67[11]	45[12]	22[13]	
Units: Months				
arithmetic mean (confidence interval 95%)	62.8 (49.0 to 73.8)	64.5 (47.3 to 77.3)	59.1 (34.5 to 77.1)	

Notes:

[11] - The per-protocol set consisted of 67 patients.

[12] - The per-protocol set of P-R consisted of 45 patients.

[13] - The per-protocol set of P-NR consisted of 22 patients.

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life at BL

End point title	Quality of life at BL

End point description:

EORTC-QLQC30

End point type	Secondary

End point timeframe:

Measured at baseline

End point values	Responder	Non-responder		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45[14]	22[15]		
Units: points				
arithmetic mean (standard deviation)	80.7 (± 14.5)	88.6 (± 9.5)		

Notes:

[14] - The per-protocol set of P-R consisted of 45 patients.

[15] - The per-protocol set of P-NR consisted of 22 patients.

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life at 24 Months

End point title	Quality of life at 24 Months

End point description:

End point type	Secondary

End point timeframe:

Measured at 24 Months

End point values	Responder	Non-responder		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45[16]	22[17]		
Units: points				
arithmetic mean (standard deviation)	68.3 (± 21.9)	67.5 (± 15.7)		

Notes:

[16] - The per-protocol set of P-R consisted of 45 patients.

[17] - The per-protocol set of P-NR consisted of 22 patients.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Reporting of AEs / SAEs begins with the inclusion of the patient in the study and ends 3 months after the operation or after (premature) termination of the study participation.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	All patients

Reporting group description:

single arm, therapeutic explorative phase II clinical multi-center trial

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 75 (21.33%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Intra-abdominal haematoma			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 75 (2.67%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Diaphragmatic abnormal relaxation				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epistaxis				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	2 / 75 (2.67%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	2 / 75 (2.67%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	1 / 1			
Pulmonary embolism				
subjects affected / exposed	3 / 75 (4.00%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Investigations				
C-reactive protein increased				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gamma-glutamyltransferase increased				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemoglobin decreased				

subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Critical illness polyneuropathy			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	2 / 75 (2.67%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	2 / 75 (2.67%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis ischaemic			

subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dysphagia			
subjects affected / exposed	5 / 75 (6.67%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 0		
Mechanical ileus			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
gallbladder perforation			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic failure			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal infarct			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue			

disorders			
critical illness myopathy			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Erysipelas			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 75 (2.67%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	2 / 75 (2.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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	47 / 75 (62.67%)		
Injury, poisoning and procedural complications			
Anastomotic complication			
subjects affected / exposed	6 / 75 (8.00%)		
occurrences (all)	6		
Nervous system disorders			

Polyneuropathy subjects affected / exposed occurrences (all)	12 / 75 (16.00%) 13		
Blood and lymphatic system disorders Leukopenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	 7 / 75 (9.33%) 7 4 / 75 (5.33%) 4		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Mucosal inflammation subjects affected / exposed occurrences (all)	 4 / 75 (5.33%) 5 4 / 75 (5.33%) 4		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Dysphagia subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	 7 / 75 (9.33%) 9 6 / 75 (8.00%) 7 11 / 75 (14.67%) 13		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 September 2014	change of inclusion criteria to include elderly patients
22 September 2015	ÖGD and PET can be done on the same day; added routine medication (mFOLFOX); additional deputy coordinating investigator and PI
02 November 2017	prolongation of recruitment period; increase of sample size from 75 to 120; additional clinical trial site Köln Recruitment was preliminarily stopped 29.08.2018 due to emerging new routine therapeutic regimen expected to impact ratio PET-responder vs PET-non-responder and improve rate of complete remissions. Follow-up of already included patients was conducted as originally planned.

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.

While results are promising, significance could not be demonstrated. The response rate was higher than originally assumed due to the emergence of new standard therapy regimen during the course of the clinical trial (premature discontinuation).

Notes: