Clinical trial results:
RE-ExPEL
A pilot study of ramucirumab beyond progression plus TAS-102 in patients with advanced or metastatic adenocarcinoma of the stomach or the gastroesophageal junction, after treatment failure on a ramucirumab based therapy

Summary

EudraCT number	2020-001075-32
Trial protocol	DE
Global end of trial date	20 January 2023

Results information

Result version number	v1 (current)
This version publication date	20 September 2023
First version publication date	20 September 2023

Trial information

Trial identification

Sponsor protocol code	RE-ExPEL

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04517747
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest
Sponsor organisation address	Steinbacher hohl 2-26, Frankfurt am Main, Germany, 60488
Public contact	Dr. Claudia Pauligk, Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest, info@ikf-khnw.de
Scientific contact	Dr. Claudia Pauligk, Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest, info@ikf-khnw.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	03 February 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 January 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether a combination of ramucirumab, beyond progression after a SOC 2nd line ramucirumab based pre-treatment (Ram beyond progression) in patients with locally advanced or metastatic adenocarcinoma, plus TAS-102 shows good tolerability without safety issues regarding the serious adverse event rate of any cause.

Protection of trial subjects:

This clinical study was designed and shall be implemented and reported in accordance with the protocol, the AMG (Arzneimittelgesetz), the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki. The trial was authorized/approved by the competent authority (Paul-Ehrlich-Institut, PEI) and the competent ethics committee responsible for the trial ("federführende Ethikkommission"). Before recruitment into the clinical trial, each patient was informed that participation in the study is completely voluntary, and that he or she may withdraw his or her participation in the trial at any time without any declaration of reasons, which will not lead to any disadvantage for the respective patient. The eligibility of a new patient was determined by the local investigator during regular clinical visits. The examinations for the study and the inclusion of the patient were done after detailed written and oral education about aims, methods, anticipated benefits and potential hazards of the study by use of the informed consent forms and after given written consent of the patient. Safety was monitored continuously by careful monitoring of all adverse events (AEs) and serious adverse events (SAEs) reported.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 October 2020
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	Germany: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

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)	20
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited by the investigator during regular clinical visits in registered trial sites. Recruitment to the study started on October 28th, 2020 and ended on August 11th, 2021. A total of 22 patients was screened and 20 patients from a total of 3 different study sites were enrolled.

Pre-assignment

Screening details:

Eligible patients were ≥18years, had histologically confirmed locally advanced or metastatic gastroesophagal adenocarcinoma and showed disease progression during or within 4-6 weeks after the last dose of a ramucirumab based 2nd line therapy and had ECOG ≤2.

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

Arm title	Experimental Arm

Arm description:

patients received ramucirumab plus TAS-102 for a maximum of 4 cycles (approx. 4months), whereat TAS-102 was prescribed and administered within its label and according to clinical routine and thus represents Standard of Care (SOC) treatment

Arm type	Experimental
Investigational medicinal product name	Ramucirumab
Investigational medicinal product code	
Other name	IMC-1121B, Cyramza
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion , Intravenous use

Dosage and administration details:

8 mg/kg, i.v. on day 1 and day 15 of a 28-day cycle

Investigational medicinal product name	TAS-102
Investigational medicinal product code	
Other name	Trifluridine/tipiracil, Lonsurf
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

35 mg/m2 p.o., twice daily on day 1 to 5 and day 8 to 12 of a 28-day cycle

Number of subjects in period 1	Experimental Arm
Started	20
Completed	6
Not completed	14
Consent withdrawn by subject	2
Lack of efficacy	12

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial (overall period)

Reporting group description: -

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	20	20	
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	56.5		
full range (min-max)	36 to 70	-	
Gender categorical Units: Subjects			
Female	4	4	
Male	16	16	
Primary localization Units: Subjects			
AEG I	7	7	
AEG II	7	7	
AEG III	2	2	
Stomach	4	4	
Histology acc. Lauren Units: Subjects			
Diffuse	3	3	
Intestinal	6	6	
Mixed	1	1	
Missing	10	10	
Histopathological Grade Units: Subjects			
G1	1	1	
G2	9	9	
G3	10	10	
ECOG performance status Units: Subjects			
ECOG 0	11	11	

ECOG 1	9	9	

End points

End points reporting groups

Reporting group title	Experimental Arm

Reporting group description:

patients received ramucirumab plus TAS-102 for a maximum of 4 cycles (approx. 4months), whereat TAS-102 was prescribed and administered within its label and according to clinical routine and thus represents Standard of Care (SOC) treatment

Primary: Rate of serious adverse events

End point title	Rate of serious adverse events[1]

End point description:

End point type	Primary

End point timeframe:

from the date the patient has received the first therapy dose and up to 30 days after the end of the last treatment cycle

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: In this pilot phase only 20 patients were treated with the combination therapy for tolerability and safety assessment of the combination of TAS-102 plus ramucirumab beyond progression with the aim of generating sufficient data to allow for the decision on a possible continuation in a randomized study. The evaluation was purely descriptive, and the primary endpoint therefore was not statistically evaluated.

End point values	Experimental Arm			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: percent				
number (confidence interval 95%)	25 (8.7 to 49.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Patients having grade 3 or more AEs for febrile neutropenia or neutrophil count decreased

End point title	Patients having grade 3 or more AEs for febrile neutropenia or neutrophil count decreased

End point description:

End point type	Secondary

End point timeframe:

from the date the patient has received the first therapy dose and up to 30 days after the end of the last treatment cycle

End point values	Experimental Arm			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Subjects				
Yes	6			
No	14			

Statistical analyses

No statistical analyses for this end point

Secondary: Patients having grade 3 or more AEs for anemia

End point title	Patients having grade 3 or more AEs for anemia

End point description:

End point type	Secondary

End point timeframe:

from the date the patient has received the first therapy dose and up to 30 days after the end of the last treatment cycle

End point values	Experimental Arm			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Subjects				
Yes	1			
No	19			

Statistical analyses

No statistical analyses for this end point

Secondary: Patients having grade 3 or more AEs for leukopenia

End point title	Patients having grade 3 or more AEs for leukopenia

End point description:

End point type	Secondary

End point timeframe:

from the date the patient has received the first therapy dose and up to 30 days after the end of the last treatment cycle

End point values	Experimental Arm			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Subjects				
Yes	3			
No	17			

Statistical analyses

No statistical analyses for this end point

Secondary: Patients having grade 3 or more AEs for thrombocytopenia

End point title	Patients having grade 3 or more AEs for thrombocytopenia

End point description:

End point type	Secondary

End point timeframe:

from the date the patient has received the first therapy dose and up to 30 days after the end of the last treatment cycle

End point values	Experimental Arm			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Subjects				
Yes	1			
No	19			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

End point title	Progression-free survival

End point description:

If no information will be available for the evaluation of progression, patients will be censored at the timepoint of last tumor assessment

End point type	Secondary

End point timeframe:

from enrollment to the first documented evidence of disease progression or death from any cause

End point values	Experimental Arm			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: month				
median (confidence interval 95%)	2.9 (1.74 to 4.80)			

Attachments (see zip file)	PFS/Progression free survival 9.1.png

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

End point type	Secondary

End point timeframe:

from enrollment to the date of death from any cause

End point values	Experimental Arm			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: month				
median (confidence interval 95%)	9.1 (5.42 to 10.09)			

Attachments (see zip file)	OS/Overall survival 9.2.png

Statistical analyses

No statistical analyses for this end point

Secondary: Best overall response

End point title	Best overall response

End point description:

tumor assessment was performed q8w during the study treatment and q12w in the follow-up

End point type	Secondary

End point timeframe:

from start of treatment to the first documented evidence of disease progression

End point values	Experimental Arm			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Subjects				
Stable disease	9			
Progressive disease	8			
Missing/ not evaluable	3			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

from the date the patient has received the first therapy dose and up to 30 days after the end of the last treatment cycle

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	5.0

Reporting groups

Reporting group title	Safety population

Reporting group description:

All patients who receive at least one dose of study medication will be included in the safety analyses

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 20 (25.00%)		
number of deaths (all causes)	13		
number of deaths resulting from adverse events	1		
General disorders and administration site conditions			
Fever			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malaise			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ileus	Additional description: subileus		
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Worsening of Enterothorax			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Bronchitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Infections and infestations			
Salivary gland infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 20 (95.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Thrombosis	Additional description: V. subclavia		
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		

Surgical and medical procedures Port dislocation subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1		
General disorders and administration site conditions Chills subjects affected / exposed occurrences (all) Edema limbs subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Fever subjects affected / exposed occurrences (all) Flu like symptoms subjects affected / exposed occurrences (all) Malaise subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all) General physical health deterioration subjects affected / exposed occurrences (all) Poor tolerance subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 6 / 20 (30.00%) 6 1 / 20 (5.00%) 2 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 2 / 20 (10.00%) 2 2 / 20 (10.00%) 2 1 / 20 (5.00%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1		

Dyspnoea subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 2		
Epistaxis subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Investigations C-reactive protein increased subjects affected / exposed occurrences (all)	4 / 20 (20.00%) 5		
Neutrophil count decreased subjects affected / exposed occurrences (all)	8 / 20 (40.00%) 9		
Platelet count decreased subjects affected / exposed occurrences (all)	4 / 20 (20.00%) 6		
Weight loss subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
White blood cell count decreased subjects affected / exposed occurrences (all)	6 / 20 (30.00%) 6		
Nervous system disorders Worsening tumor pain subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	6 / 20 (30.00%) 7		
Gastrointestinal disorders Abdominal pain			

subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	4		
Ascites			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Constipation			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Dysphagia			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	5		
Vomiting			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Redness of port region			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Proteinuria			

subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Infections and infestations Bronchial infection subjects affected / exposed occurrences (all) Infection unknown origin subjects affected / exposed occurrences (all) Lung infection subjects affected / exposed occurrences (all) Mucosal infection subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 1 / 20 (5.00%) 2 1 / 20 (5.00%) 1		
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all)	 3 / 20 (15.00%) 3 1 / 20 (5.00%) 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? No

Limitations and caveats

None reported