Clinical trial results:
A randomized, multicenter open label phase II trial of Paclitaxel + Ramucirumab versus Paclitaxel alone in patients with squamous-cell carcinoma of the esophagus, refractory or intolerant to combination therapy with Fluoropyrimidine or Platinum-based drugs

Summary

EudraCT number	2016-003850-33
Trial protocol	DE
Global end of trial date	25 November 2022
Results information	
Result version number	v1 (current)
This version publication date	28 October 2023
First version publication date	28 October 2023

Trial information

Trial identification	
Sponsor protocol code	RAMOS
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03762564
WHO universal trial number (UTN)	-
Other trial identifiers	AIO-STO-0216/ass: AIO

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, ramos@ikf-khnw.de
Scientific contact	Dr. Claudia Pauligk, Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest, ramos@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	05 January 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 October 2021
Global end of trial reached?	Yes
Global end of trial date	25 November 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of ramucirumab plus paclitaxel versus paclitaxel alone measured by overall survival rate at 6 months in patients with squamous cell carcinoma of the esophagus refractory or intolerant to combination therapy with fluoropyrimidine and platinum-based drugs.

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 of paclitaxel alone or in combination with ramucirumab was monitored continuously by careful monitoring of all adverse
events (AEs) and serious adverse events (SAEs) reported. An independent data safety monitoring board (DSMB) was responsible for assessment of reports summarizing safety data or study results and gave recommendations for planned protocol.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 December 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 21
Worldwide total number of subjects	21
EEA total number of subjects	21

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)	12
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

186 patients for were planned. Due to slow recruitment and changes in the therapy landscape the trial was prematurely terminated.
The recruitment period was 28 months, March 2019 - June 2021 and took place in 26 centers in Germany.

Pre-assignment

Screening details:

patients with metastatic or locally advanced squamous-cell carcinoma of the esophagus, refractory to or intolerant of prior platinum and fluoropyrimidine combination therapy were enrolled

27 patients were screened, 6 were refused participation due to ineligibility of inclusion/exclusion criteria

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Investigational arm

Arm description:

Patients received paclitaxel in combination with ramucirumab

Arm type	Experimental
Investigational medicinal product name	Ramucirumab
Investigational medicinal product code	
Other name	CYRAMZA
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use, Infusion

Dosage and administration details:

8 mg/kg as 1 hour intravenous infusion on day 1 and 15 of each 28-day cylce; for up to one year

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion , Intravenous use

Dosage and administration details:

80 mg/m2 as 1 hour intravenous infusion on day 1, 8, 15 of each 28-day cycle, for up to one year

Arm title	Control arm

Arm description:

Patients received paclitaxel monotherapy

Arm type	Active comparator
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion , Intravenous use

Dosage and administration details:

80 mg/m2 as 1 hour intravenous infusion on day 1, 8, 15 of each 28-day cycle, for up to one year

Number of subjects in period 1	Investigational arm	Control arm
Started	11	10
Completed	1	0
Not completed	10	10
Consent withdrawn by subject	2	1
Adverse event, non-fatal	1	-
Death	1	-
Lack of efficacy	6	9

Baseline characteristics

Reporting groups	
Reporting group title	Investigational arm
Reporting group description:	
Patients received paclitaxel in combination with ramucirumab	
Reporting group title	Control arm
Reporting group description:	
Patients received paclitaxel monotherapy	

Reporting group values	Investigational arm	Control arm	Total
Number of subjects	11	10	21
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	66	62	
full range (min-max)	43 to 76	56 to 68	-
Gender categorical Units: Subjects			
Female	4	2	6
Male	7	8	15
ECOG Performance Units: Subjects			
Status 0	4	6	10
Status 1	7	4	11
Tumor localization Units: Subjects			
Upper esophagus	5	4	9
Middle esophagus	5	3	8
Lower esophagus	1	3	4
Presence of metastases (at study entry) Units: Subjects			
NO	1	2	3
YES	10	8	18
Status of prior platinum/fluoropyrimidine combination therapy Units: Subjects			

Refractory	9	7	16
Intolerant	2	3	5
Prior resection Units: Subjects			
Of primary tumor	2	5	7
Of metastases	0	1	1
NO	9	4	13

End points

End points reporting groups	
Reporting group title	Investigational arm
Reporting group description:	
Patients received paclitaxel in combination with ramucirumab	
Reporting group title	Control arm
Reporting group description:	
Patients received paclitaxel monotherapy	

Primary: Overall survival rate at 6 months	
End point title	Overall survival rate at 6 months
End point description:	
defined at the proportion of all intention-to-treat patients being known to be alive at 6 months after randomisation	
End point type	Primary
End point timeframe:	
from randomisation to 6 months after randomisation	

End point values	Investigational arm	Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: percent				
number (confidence interval 95%)				
Alive	72.7 (39 to 94)	50 (19 to 81)		

Statistical analyses

Statistical analysis title	Fisher exact test
Comparison groups	Investigational arm v Control arm
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.387
Method	Fisher exact

Secondary: Progression-free survival	
End point title	Progression-free survival
End point description:	
Patients without any documentation of events are censored at their date of end of study respectively at	

the last date known to be progression-free

End point type	Secondary

End point timeframe:

from randomization to the first documented evidence of disease progression or death

End point values	Investigational arm	Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: month				
median (confidence interval 95%)				
median PFS	3.79 (0.69 to 7.56)	3.53 (1.51 to 5.59)		

Attachments (see zip file)	RAMOS PFS.png

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Patients without any documentation of events are censored at their date of end of study respectively at the last date known to be alive.

End point type	Secondary

End point timeframe:

from randomization to death from any cause

End point values	Investigational arm	Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: month				
median (confidence interval 95%)				
median OS	12.09 (3.29 to 9999999)	9.22 (2.00 to 99999999)		

Attachments (see zip file)	RAMOS OS.png

Statistical analyses

No statistical analyses for this end point

Secondary: Tumor response acc. to RECIST 1.1

End point title	Tumor response acc. to RECIST 1.1

End point description:

End point type	Secondary

End point timeframe:
from randomization to end of study

End point values	Investigational arm	Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: Subjects				
Complete response (CR)	0	0		
Partial response (PR)	2	2		
Stable disease (SD)	4	4		
Progressive diesase (PD)	3	4		
Objective response rate (CR+PR)	2	2		
Tumor control rate (CR + PR + SD)	6	6		
Missing	2	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: from signing of informed consent up to 30 days after last dose of study treatment	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	4

Reporting groups	
Reporting group title	Investigational arm
Reporting group description: Patients received paclitaxel in combination with ramucirumab	
Reporting group title	Control arm
Reporting group description: Patients received paclitaxel monotherapy	

Serious adverse events	Investigational arm	Control arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 11 (36.36%)	5 / 10 (50.00%)	
number of deaths (all causes)	6	6	
number of deaths resulting from adverse events	0	1	
Investigations			
Hospitalization due to vomiting			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Progressive disease			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Stenosis	Additional description: Left leg		
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Oesophageal fistula			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Other	Additional description: Recurrence of purulent respiratory tract infection under oncological systemic therapy		
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pain lumbar vertebra			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchial infection			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			

subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Origin unknown infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 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	Investigational arm	Control arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 11 (100.00%)	10 / 10 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumor pain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Edema limbs			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Fatigue			

subjects affected / exposed	2 / 11 (18.18%)	4 / 10 (40.00%)	
occurrences (all)	2	7	
Fever			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Other	Additional description: toxicity, Hematoxic		
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
ankle edema			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Pain			
subjects affected / exposed	1 / 11 (9.09%)	2 / 10 (20.00%)	
occurrences (all)	1	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Dyspnoea			
subjects affected / exposed	2 / 11 (18.18%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	3	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Other	Additional description: pressure on the upper abdomen		
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Neutropenia			
subjects affected / exposed	1 / 11 (9.09%)	4 / 10 (40.00%)	
occurrences (all)	1	8	
Thrombocytopenia			

subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Weight increased			
subjects affected / exposed	0 / 11 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
Weight decreased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Leukopenia			
subjects affected / exposed	6 / 11 (54.55%)	4 / 10 (40.00%)	
occurrences (all)	10	17	
Injury, poisoning and procedural complications			
Cat Bite			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 11 (18.18%)	2 / 10 (20.00%)	
occurrences (all)	4	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 11 (9.09%)	4 / 10 (40.00%)	
occurrences (all)	3	9	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 11 (9.09%)	2 / 10 (20.00%)	
occurrences (all)	1	2	
Diarrhoea			
subjects affected / exposed	1 / 11 (9.09%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Dysphagia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Oesophageal stenosis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	

Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Other	Additional description: occasional running bowel movement		
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Mucositis oral			
subjects affected / exposed	2 / 11 (18.18%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Nausea			
subjects affected / exposed	0 / 11 (0.00%)	3 / 10 (30.00%)	
occurrences (all)	0	3	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 11 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
Rash acneiform			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Exanthem nose			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Proteinuria			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 11 (9.09%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Back pain			
subjects affected / exposed	0 / 11 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	

Joint pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
lumbar vertebra pain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Neck pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Bronchial infection			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Port infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Lung infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 March 2020	- Opening of the study (inclusion criterion 3) to patients who are refractory or intolerant to fluoropyrimidine OR platinum-based prior therapy - Exclusion criterion 2: no exclusion of patient who receives additive parenteral nutrition - Deletion of exclusion criterion 3 - Exclusion criterion 4: limitation to Paclitaxel prior therapies in metastatic setting
04 June 2020	Reformulation Inclusion criterion 2: "Adult patients with metastatic or locally advanced squamous-cell carcinoma of the esophagus, not amenable to potentially curative resection, who are refractory to or intolerant of prior platinum and fluoropyrimidine combination therapy. An exception are patients with a contraindication for platinum or fluoropyrimidine or who refused therapy with one of the substances. Those patients are eligible after previous therapy with one of the substances."

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported