Clinical trial results:
Avelumab + Paclitaxel/ Ramucirumab as second line treatment in gastro-esophageal adenocarcinoma: a phase II trial of the AIO. The RAP-Trial.

Summary

EudraCT number	2018-002938-20
Trial protocol	DE
Global end of trial date	29 November 2022

Results information

Result version number	v1 (current)
This version publication date	27 January 2024
First version publication date	27 January 2024

Trial information

Trial identification

Sponsor protocol code	AIO-STO-0218

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03966118
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Charité - Universitätsmedizin Berlin
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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	14 December 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 November 2022
Global end of trial reached?	Yes
Global end of trial date	29 November 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary clinical objective is to determine the efficacy of a standard second-line regimen (paclitaxel + ramucirumab) with avelumab in patients with metastatic gastro-oesophageal cancer in terms of overall survival rate (OSR) at 6 months (according to RECIST v1.1).

Protection of trial subjects:

The responsible investigator ensured that this study is conducted in agreement with either the Declaration of Helsinki (in its current version) or the laws and regulations in its current version.
Safety assessments will include physical examinations including vital signs (blood pressure, heart rate), performance status (ECOG), clinical laboratory profile, concomitant medication and adverse events.
All observed toxicities and side effects will be graded according to NCI CTCAE v5.0 (NCI 2018) for all patients. The adverse events will also be analysed in accordance to their relation to the study treatment.
Treatment related serious adverse events rate (SAE), defined as SAEs considered possibly, probably or definitely related to treatment, will be determined.

Background therapy:

Second-line chemotherapy prolongs survival in metastatic gastro-esophageal cancer compared to best supportive care. In the RAINBOW trial (Wilke et al. 2014; Shitara et al. 2016) ramucirumab + paclitaxel was compared to placebo + paclitaxel and showed an improvement of response rate and overall survival.PD-1 and PD-L1 inhibitors are a very promising treatment option in gastro-esophageal adenocarcinoma, but currently there are no treatment options incorporating PD-1 blockade in the second line setting in gastro-esophageal adenocarcinomas .
Due to these reasons a combination of PD-L1 inhibition with the best established second line chemotherapy (paclitaxel+ramucirumab) is the logical next step to improve survival of metastatic gastric cancer patients and to establish PD-L1 blockade in the second line setting in combination with the currently available best second line regimen.

Evidence for comparator: -

Actual start date of recruitment	20 March 2019
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: 60
Worldwide total number of subjects	60
EEA total number of subjects	60

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)	30
From 65 to 84 years	30
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 13 study sites in Germany, between Date (15/05/2019) and Date (06/11/2020). Only in 10 study sites were patients recruited.

Pre-assignment

Screening details:

According the inclusion and exclusion criteria gastric/GEJ adenocarcinoma adult patients with documented objective radiological or clinical disease progression during or within 6 months of the last dose of first-line platinum and fluoropyrimidine doublet with or without anthracycline, docetaxel or trastuzumab were 60 patients recruited.

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, multicenter phase II trial designed to assess the clinical performance of avelumab in combination with paclitaxel and ramucirumab as second-line treatment in patients with gastric or gastro-oesohageal junction adenocarcinoma.

Arms

Arm title	Standard Regime + Avelumab

Arm description:

This is a single arm, multicenter phase II trial designed to assess the clinical performance of avelumab in combination with paclitaxel and ramucirumab as second-line treatment in patients with gastric or gastro-oesohageal junction adenocarcinoma. The dose of the therapy is dependent upon the patient's baseline body weight in kilograms and the body surface. Premedication 30 to 60 minutes prior to the first 4 infusions of avelumab is mandatory. A premedication with antihistamine (for example 4 mg dimetindenmaleat), H2 blocker (for example 50mg ranitidin), 500 mg paracetamol i.v. or oral, 10 mg dexamethason before treatment infusion. Avelumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment After adimistration of avelumab there must be a break of at least 30 minutes before therapy with ramucirumab is given. Also for ramucirumab a premedication with an antihistamine is recommended.

Arm type	Experimental
Investigational medicinal product name	AVELUMAB
Investigational medicinal product code	SUB180078
Other name	Bavencio
Pharmaceutical forms	Infusion
Routes of administration	Concentrate for solution for infusion

Dosage and administration details:

Avelumab at a dose of 10 mg/kg will be given by i.v. infusion over 60 to 90 min on day 1 and 15 of a 28-day cycle.

Investigational medicinal product name	Ramucirumab
Investigational medicinal product code	SUB32795
Other name	Cyramza
Pharmaceutical forms	Infusion
Routes of administration	Concentrate for solution for infusion

Dosage and administration details:

Ramucirumab at dose of 8 mg/kg will be given by i.v. infusion over 60 minutes on day 1 and 15 of a 28-day cycle.

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	SUB09583MIG
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Concentrate for solution for infusion

Dosage and administration details:

Paclitaxel at a dose of 80 mg/m2 will be given by i.v. infusion over 60 minutes on day 1, 8 and 15 of a 28-day cycle.

Number of subjects in period 1	Standard Regime + Avelumab
Started	60
Completed	40
Not completed	20
Adverse event, serious fatal	5
Consent withdrawn by subject	1
Physician decision	2
progress disease	12

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	60	60	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	30	30	
From 65-84 years	30	30	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	12	12	
Male	48	48	

End points

End points reporting groups

Reporting group title	Standard Regime + Avelumab

Reporting group description:

This is a single arm, multicenter phase II trial designed to assess the clinical performance of avelumab in combination with paclitaxel and ramucirumab as second-line treatment in patients with gastric or gastro-oesohageal junction adenocarcinoma. The dose of the therapy is dependent upon the patient's baseline body weight in kilograms and the body surface. Premedication 30 to 60 minutes prior to the first 4 infusions of avelumab is mandatory. A premedication with antihistamine (for example 4 mg dimetindenmaleat), H2 blocker (for example 50mg ranitidin), 500 mg paracetamol i.v. or oral, 10 mg dexamethason before treatment infusion. Avelumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment After adimistration of avelumab there must be a break of at least 30 minutes before therapy with ramucirumab is given. Also for ramucirumab a premedication with an antihistamine is recommended.

Primary: survival (OS) rate at 6 month

End point title	survival (OS) rate at 6 month[1]

End point description:

End point type	Primary

End point timeframe:

The Overall Survival Rate at 6 months (primary endpoint) will be determined by the proportion of ITT patients being alive 6 months after treatment start with first day first cycle divided by the total number of ITT patients.

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: If p values are calculated (e.g. for comparison of subgroups), they will be presented explicitly without referring to hypotheses or a significance level. All p values will be two-sided .Patients with higher versus lower than median T cell repertoire richness showed an elevated median OS of 20.4 compared to 8.3 months (HR 0.43, 95% CI 0.23-0.81; p=0.008).
Patients with lower versus higher than median cfDNA burden: median OS of 19.2 compared to 7.3 months (HR 0.30, 95% CI 0.16-0.59; p<0.001).

End point values	Standard Regime + Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	59			
Units: months				
number (confidence interval 95%)				
Overall survival rate at 6 months (H0≤50%, H1≥65%)	71.2 (61.5 to 83.7)			
median OS (ITT)	10.6 (8.4 to 12.8)			
patients with PD-L1 CPS<5	9.4 (7.2 to 11.7)			
patients PD-L1 CPS≥5	14.0 (6.0 to 22.1)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During the course of the study all AEs and SAEs should be proactively followed up for each subject.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	5.0

Reporting groups

Reporting group title	Standard Regime + Avelumab

Reporting group description: -

Serious adverse events	Standard Regime + Avelumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 59 (35.59%)		
number of deaths (all causes)	7		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
hematemesis			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Meningeosis carcinomatosa			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
bleeding brain metastasis			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
thromboembolic event			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

General disorders and administration site conditions			
fever			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Enterothorax			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Investigations			
ALT increased	Additional description: Alanine transaminase (ALT)		
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutrophil count decreased			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
port/ catheter related infection			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
obstruction tracheal stent			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Peripheral sensory neuropathy			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo	Additional description: worsening of vertigo		
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ileus	Additional description: Ileus/ Ileua of small intestine/Subileus		
subjects affected / exposed	3 / 59 (5.08%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Vomiting			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Duodenal stenosis			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dysphagia	Additional description: esophagial thrush		

subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
oral hemorrhage				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
mucositis				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Hematuria				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Back pain				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neck pain	Additional description: Cervicalgie			
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Infections and infestations			
Pneumonia			
subjects affected / exposed	6 / 59 (10.17%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 1		
sepsis (abdominal/unknown focus)			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Urinary tract infection			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	Standard Regime + Avelumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 59 (66.10%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 59 (13.56%)		
occurrences (all)	13		
General disorders and administration site conditions			
Fatigue			

subjects affected / exposed	35 / 59 (59.32%)		
occurrences (all)	48		
Edema limbs			
subjects affected / exposed	8 / 59 (13.56%)		
occurrences (all)	12		
Fever			
subjects affected / exposed	9 / 59 (15.25%)		
occurrences (all)	10		
Pain	Additional description: Pain+ bone pain+ non chardiac chest pain + throat pain+ pain after radio frequency ablation		
subjects affected / exposed	13 / 59 (22.03%)		
occurrences (all)	13		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	18 / 59 (30.51%)		
occurrences (all)	23		
Dyspnea			
subjects affected / exposed	16 / 59 (27.12%)		
occurrences (all)	17		
Cough			
subjects affected / exposed	5 / 59 (8.47%)		
occurrences (all)	7		
Investigations			
Neutrophil count decreased			
subjects affected / exposed	20 / 59 (33.90%)		
occurrences (all)	45		
White blood cell count decreased	Additional description: Leucopenia		
subjects affected / exposed	20 / 59 (33.90%)		
occurrences (all)	44		
CRP increased			
subjects affected / exposed	6 / 59 (10.17%)		
occurrences (all)	7		
Nervous system disorders			
Peripheral motorsensory neuropathy			
subjects affected / exposed	26 / 59 (44.07%)		
occurrences (all)	31		
Taste disorders	Additional description: Dysgeusia+ taste disorders		

subjects affected / exposed	14 / 59 (23.73%)		
occurrences (all)	16		
Paresthesia			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	6		
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	14 / 59 (23.73%)		
occurrences (all)	14		
Leucocytosis			
subjects affected / exposed	5 / 59 (8.47%)		
occurrences (all)	6		
Ear and labyrinth disorders			
Vertigo	Additional description: Vertigo + Dizziness		
subjects affected / exposed	12 / 59 (20.34%)		
occurrences (all)	13		
Eye disorders			
vision disorders			
subjects affected / exposed	6 / 59 (10.17%)		
occurrences (all)	8		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	23 / 59 (38.98%)		
occurrences (all)	42		
Nausea			
subjects affected / exposed	20 / 59 (33.90%)		
occurrences (all)	27		
Mucositis oral			
subjects affected / exposed	14 / 59 (23.73%)		
occurrences (all)	16		
Vomiting			
subjects affected / exposed	8 / 59 (13.56%)		
occurrences (all)	15		
Dysphagia			
subjects affected / exposed	10 / 59 (16.95%)		
occurrences (all)	13		
Constipation			

subjects affected / exposed	11 / 59 (18.64%)		
occurrences (all)	11		
Abdominal/stomach/gastrointestianal pain			
subjects affected / exposed	14 / 59 (23.73%)		
occurrences (all)	15		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	23 / 59 (38.98%)		
occurrences (all)	26		
nail changes/ loss/ dystrophy			
subjects affected / exposed	7 / 59 (11.86%)		
occurrences (all)	9		
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	5 / 59 (8.47%)		
occurrences (all)	5		
Rash acneiform			
subjects affected / exposed	7 / 59 (11.86%)		
occurrences (all)	7		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	9 / 59 (15.25%)		
occurrences (all)	10		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	6 / 59 (10.17%)		
occurrences (all)	7		
Back pain	Additional description: Back+ Flank+back ribage+spinal disk area pain		
subjects affected / exposed	7 / 59 (11.86%)		
occurrences (all)	9		
Generalized muscle weakness			
subjects affected / exposed	12 / 59 (20.34%)		
occurrences (all)	14		
Infections and infestations			
Urinary tract infection			

subjects affected / exposed occurrences (all) Rash (papulopustular/pustular) subjects affected / exposed occurrences (all)	7 / 59 (11.86%) 8 7 / 59 (11.86%) 7		
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all)	 19 / 59 (32.20%) 21		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 April 2019	late registration of additional study site
23 July 2019	late registration of additional study site
08 August 2019	update Study protocol version 1.2
27 July 2020	update information about Avelimab Version 9, dated 03/06/2019 update Information about Paclitaxel and Ramucirumab (01/2020)
29 July 2020	update Investigator´s Brochure Version 11
13 June 2022	Extension of the study duration until 31/12/2022

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported