Clinical trial results:
RAMTAS
A Phase III study of RAMucirumab in combination with TAS102 vs. TAS102 monotherapy in chemotherapy refractory metastatic colorectal cancer patients

Summary

EudraCT number	2017-004162-99
Trial protocol	DE
Global end of trial date	30 July 2024

Results information

Result version number	v1 (current)
This version publication date	07 November 2025
First version publication date	07 November 2025

Trial information

Trial identification

Sponsor protocol code	RAMTAS

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03520946
WHO universal trial number (UTN)	-
Other trial identifiers	AIO number: AIO-KRK-0316/ass

Notes:

Sponsors

Sponsor organisation name	Frankfurter Institut für Klinische Krebsforschung IKF GmbH
Sponsor organisation address	Steinbacher Hohl 2-26, Frankfurt am Main, Germany,
Public contact	IKF GmbH, Frankfurter Institut für Klinische Krebsforschung IKF GmbH am , 0049 695899787-19, ramtas@ikf-khnw.de
Scientific contact	IKF GmbH, Frankfurter Institut für Klinische Krebsforschung IKF GmbH , 0049 695899787-19, ramtas@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	27 August 2025
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 July 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of ramucirumab in combination with TAS102 (Trifluridin/Tipiracil-Lonsurf®) vs. TAS102 monotherapy in patients with refractory mCRC.

Protection of trial subjects:

This clinical trial 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/Aapproved by the competent authority (Paul-Ehrlic-Institut, PEI) and the competent ethics committee responsible for the trial (“federführende Ethikkommission). Before recruitment into the clinical trial, each patient was informed That participant in the trial at any time without any declaration of reasons, which will lead to any disadvantage for the respective patient. The eligibility of a new patient was determined by the local investigator during regular visits. The examinatons 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 Ramucircumab/TAS102 was monitored continuously by careful monitoring of all adverse events (AEs) and serious adverse events (SAEs) reported. An independent data safety and monitoring board (DSMB) was responsible for assessment of reports summarizing safety data or study results and gave recommendations for planned protocol amendments.

Background therapy: -

Evidence for comparator:

TAS102 is a novel cytotoxic drug consisting of an antineoplastic nucleoside analogue (trifluridine; FTD) and a thymidine phosphorylase inhibitor (tipiracil hydrochloride; TPI). It is approved in Japan, the USA and Europe for the treatment of patients with mCRC who have been previously treated with, or are not candidates for fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and an anti-EGFR therapy (if indicated).

Ramucirumab is a human monoclonal antibody that specifically binds VEGF-R2. The binding of ramucirumab to VEGF-R2 prevents its interaction with the activating ligands VEGF-A, VEGF-C and VEGF-D. As a result, ramucirumab inhibits ligand-stimulated activation of VEGFR-2, thereby inhibiting ligand-induced proliferation, downstream signaling components including ERK1/2, and migration of human endothelial cells. Ramucirumab was approved for as second line treatment of mCRC

Actual start date of recruitment	24 January 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: 428

Worldwide total number of subjects	428
EEA total number of subjects	428

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)	248
From 65 to 84 years	175
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

Between January 2019 and February 2023, 493 patients were screened for eligibility and 430 patients were randomized in 43 trial sites. 428 patients were included in the ITT population (213 in Arm A and 215 in Arm B).

Pre-assignment

Screening details:

Patients with refractory metastatic colorectal cancer (mCRC), who have progressed on/after, did not tolerate, refuse or have contraindications to fluoropyrimidines, oxaliplatin, irinotecan, anti-angiogenic therapies (bevacizumab, aflibercept, or regorafenib) and if indicated anti-EGFR antibodies (cetuximab or panitumumab)

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Experimental Arm Ramu + TAS-102

Arm description:

Patients received ramucirumab plus TAS-102 for a maximum of 6 cycles. (approx. 6 months), whereby TAS-102 was presicribed and administered within its label and according to clinical routin and thus represents Standard of Care (SOC) treatment.

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

Dosage and administration details:

8 mg/kg, i.v., on day 1 and day 15 of a 4-week cycle [Q4W])

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, orally, twice a day on day 1 – 5 and day 8 – 12 of a 4-week cycle [Q4W]

Arm title	Control Arm TAS-102

Arm description:

TAS-102 was prescibed and administered within its label and according to clinical routine orally, twice a day, on day 1-5 and 8-12 of a 4-week cycle and thus represents Standard of Care treatment

Arm type	Active comparator

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, orally, twice a day on day 1 – 5 and day 8 – 12 of a 4-week cycle [Q4W]

Number of subjects in period 1	Experimental Arm Ramu + TAS-102	Control Arm TAS-102
Started	213	215
Completed	12	5
Not completed	201	210
Physician decision	12	10
Consent withdrawn by subject	14	16
Toxicity	11	2
Death	22	9
Other	7	6
Progressive disease	135	167

Baseline characteristics

Reporting groups

Reporting group title	Experimental Arm Ramu + TAS-102

Reporting group description:

Patients received ramucirumab plus TAS-102 for a maximum of 6 cycles. (approx. 6 months), whereby TAS-102 was presicribed and administered within its label and according to clinical routin and thus represents Standard of Care (SOC) treatment.

Reporting group title	Control Arm TAS-102

Reporting group description:

TAS-102 was prescibed and administered within its label and according to clinical routine orally, twice a day, on day 1-5 and 8-12 of a 4-week cycle and thus represents Standard of Care treatment

Reporting group values	Experimental Arm Ramu + TAS-102	Control Arm TAS-102	Total
Number of subjects	213	215	428
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	132	116	248
From 65-84 years	80	95	175
85 years and over	1	4	5
Age continuous Units: years			
median	61	63	
full range (min-max)	25 to 87	27 to 90	-
Gender categorical Units: Subjects			
Female	93	100	193
Male	120	115	235
ECOG Units: Subjects			
ECOG 0	116	110	226
ECOG 1	97	105	202
Localization of primary tumor Units: Subjects			
Ascendens	22	25	47
Coecum	27	20	47
Descendens	8	6	14
Rectum	87	69	156
Sigma	47	57	104
Transversum	8	22	30
Other	14	16	30

Localization group Units: Subjects			
Right	61	77	138
Left	149	138	287
unknown	3	0	3
T stage Units: Subjects			
T1	6	9	15
T2	10	10	20
T3	109	118	227
T4	63	57	120
Tx	25	21	46
N stage Units: Subjects			
N0	43	52	95
N+	169	162	331
Missing	1	1	2
M stage Units: Subjects			
M0	11	7	18
M1	202	208	410
Histopathological grade Units: Subjects			
G1	5	7	12
G2	140	149	289
G3	47	29	76
unknown	21	30	51
No. of organs with metastases Units: Subjects			
1 organ	37	61	98
>1 organ	165	147	312
Unknown	11	7	18
Duration of previous anti-angiogenic therapies Units: Subjects			
< 12 months	139	141	280
> 12 months	74	74	148
RAS mutational status Units: Subjects			
Mutation	133	131	264
Wildtype	80	84	164
BRAF V600E mutational status Units: Subjects			
Mutation	8	11	19
Wildtype	205	204	409

End points

End points reporting groups

Reporting group title	Experimental Arm Ramu + TAS-102

Reporting group description:

Patients received ramucirumab plus TAS-102 for a maximum of 6 cycles. (approx. 6 months), whereby TAS-102 was presicribed and administered within its label and according to clinical routin and thus represents Standard of Care (SOC) treatment.

Reporting group title	Control Arm TAS-102

Reporting group description:

TAS-102 was prescibed and administered within its label and according to clinical routine orally, twice a day, on day 1-5 and 8-12 of a 4-week cycle and thus represents Standard of Care treatment

Subject analysis set title	ITT Arm A
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intent-to-treat (ITT) population included all randomized patients. Treatment assignment was based on the randomized treatment (primary population). The ITT population is the primary population for the description of the patient and treatment characteristics and was used for the primary efficacy analysis.

Subject analysis set title	ITT Arm B
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intent-to-treat (ITT) population included all randomized patients. Treatment assignment was based on the randomized treatment (primary population). The ITT population is the primary population for the description of the patient and treatment characteristics and was used for the primary efficacy analysis.

Subject analysis set title	PP Arm A
Subject analysis set type	Per protocol

Subject analysis set description:

This population included all randomized patients fulfilling the inclusion (except life expectancy of at least 3 months) and exclusion criteria and who received at least one cycle of the treatment. Treatment assignment was based on the treatment actually received.

Subject analysis set title	PP Arm B
Subject analysis set type	Per protocol

Subject analysis set description:

This population included all randomized patients fulfilling the inclusion (except life expectancy of at least 3 months) and exclusion criteria and who received at least one cycle of the treatment. Treatment assignment was based on the treatment actually received.

Subject analysis set title	Safety Analysis Set Arm A
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety set was used for all safety endpoints and comprised all patients randomized who received at least one dose of study treatment. Patients were analyzed according to the treatment actually received.

Subject analysis set title	Safety Analysis Set Arm B
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety set was used for all safety endpoints and comprised all patients randomized who received at least one dose of study treatment. Patients were analyzed according to the treatment actually received.

Primary: Overall Survival

End point title	Overall Survival

End point description:

End point type	Primary

End point timeframe:

time from randomization until death from any cause. If no event was observed (e.g., lost to follow-up) OS was censored at the day of last subject contact

End point values	ITT Arm A	ITT Arm B	PP Arm A	PP Arm B
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	213	215	209	209
Units: months				
median (confidence interval 95%)				
Overall Survival	7.5 (6.2 to 8.6)	7.1 (6.0 to 8.3)	7.5 (6.4 to 8.6)	7.1 (6.1 to 8.4)

Statistical analyses

Statistical analysis title	Log Rank Test
Comparison groups	ITT Arm B v ITT Arm A
Number of subjects included in analysis	428
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2516
Method	Logrank

Statistical analysis title	Log Rank Test
Comparison groups	PP Arm A v PP Arm B
Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2627
Method	Logrank

Secondary: Progression free survival

End point title	Progression free survival

End point description:

End point type	Secondary

End point timeframe:

time from randomization to the first occurrence of progression, as determined by the investigator using CT criteria, or death from any cause. If no event was observed (e.g., lost to follow-up) PFS was censored at the time of last tumor assessment.

End point values	ITT Arm A	ITT Arm B	PP Arm A	PP Arm B
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	213	215	209	209
Units: months				
median (confidence interval 95%)				
PSF	2.4 (2.1 to 3.0)	2.1 (2.0 to 2.1)	2.4 (2.07 to 2.96)	2.1 (2.0 to 2.1)

Statistical analyses

Statistical analysis title	Log Rank Test
Comparison groups	ITT Arm A v ITT Arm B
Number of subjects included in analysis	428
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0035
Method	Logrank

Statistical analysis title	Log Rank Test
Comparison groups	PP Arm A v PP Arm B
Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0047
Method	Logrank

Secondary: OS rate 6 and 12 months

End point title	OS rate 6 and 12 months

End point description:

End point type	Secondary

End point timeframe:

percentage of patients being alive 6 and 12 months, respectively, after randomization.

End point values	ITT Arm A	ITT Arm B	PP Arm A	PP Arm B
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	213	215	209	209
Units: %				
OS@6	59	57	60	58
OS@12	31	26	31	27

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate

End point title	Objective response rate

End point description:

End point type	Secondary

End point timeframe:

proportion of patients whose best overall response (BOR) from baseline was either a complete (CR) or partial response (PR) per RECIST 1.1 criteria.

End point values	ITT Arm A	ITT Arm B	PP Arm A	PP Arm B
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	213	215	209	209
Units: %				
Objective response rate	2	2	2	2

Statistical analyses

Statistical analysis title	Fishers Exact Test
Comparison groups	ITT Arm A v ITT Arm B
Number of subjects included in analysis	428
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1
Method	Fisher exact

Statistical analysis title	Fishers Exact Test
Comparison groups	PP Arm A v PP Arm B

Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1
Method	Fisher exact

Secondary: Disease control rate

End point title	Disease control rate

End point description:

End point type	Secondary

End point timeframe:
proportion of patients with CR or PR or stable disease (SD) per RECIST 1.1 criteria.

End point values	ITT Arm A	ITT Arm B	PP Arm A	PP Arm B
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	213	215	209	209
Units: %				
DCR	40	32	41	33

Statistical analyses

Statistical analysis title	Fischers Exact Test
Comparison groups	ITT Arm A v ITT Arm B
Number of subjects included in analysis	428
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0341
Method	Fisher exact

Statistical analysis title	Fischers Exact Test
Comparison groups	PP Arm A v PP Arm B
Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0343
Method	Fisher exact

Secondary: Best overall response

End point title	Best overall response

End point description:

End point type	Secondary

End point timeframe:

best overall response (BOR) from baseline per RECIST 1.1 criteria

End point values	ITT Arm A	ITT Arm B	PP Arm A	PP Arm B
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	213	215	209	209
Units: Patients				
Complete response	0	0	0	0
Partial response	4	4	4	4
Stable disease	81	64	81	64
Progressive disease	94	120	94	119
Missing	34	27	30	22

Statistical analyses

No statistical analyses for this end point

Secondary: Efficay in patients with neutropenia

End point title	Efficay in patients with neutropenia

End point description:

End point type	Secondary

End point timeframe:

ORR and DCR in patients who developed neutropenia grade ≥2 (ANC ≤1500/µl) in cycle 1

End point values	ITT Arm A	ITT Arm B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52	44		
Units: %				
ORR	2	0		
DCR	40	48		

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life @ 4 weeks

End point title	Quality of Life @ 4 weeks

End point description:

End point type	Secondary

End point timeframe:

Quality of life (QoL) was assessed every 4 weeks during therapy using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC-QLQ-C30) and the EuroQol 5 dimensions 5-level version (EQ-5D-5L). QoL response wa

End point values	ITT Arm A	ITT Arm B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	157	162		
Units: patients				
Missing	23	11		
Deteriorated	34	43		
Stable	78	80		
Improved	22	28		

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life @ 8 weeks

End point title	Quality of Life @ 8 weeks

End point description:

End point type	Secondary

End point timeframe:

Quality of life (QoL) was assessed every 4 weeks during therapy using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC-QLQ-C30) and the EuroQol 5 dimensions 5-level version (EQ-5D-5L). QoL response wa

End point values	ITT Arm A	ITT Arm B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	157	162		
Units: patients				
Missing	53	60		
Deteriorated	44	36		
Stable	43	44		
Improved	17	22		

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life @ 12 weeks

End point title	Quality of Life @ 12 weeks

End point description:

End point type	Secondary

End point timeframe:

Quality of life (QoL) was assessed every 4 weeks during therapy using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC-QLQ-C30) and the EuroQol 5 dimensions 5-level version (EQ-5D-5L).

End point values	ITT Arm A	ITT Arm B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	157	162		
Units: patients				
Missing	96	119		
Deteriorated	21	14		
Stable	30	21		
Improved	10	8		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

after patient has given written informed consent until at least 30 days after the last dose of study treatment

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Safety analysis set Arm A
Reporting group description: -	
Reporting group title	Safety analysis set Arm B

Reporting group description: -

Serious adverse events	Safety analysis set Arm A	Safety analysis set Arm B	
Total subjects affected by serious adverse events			
subjects affected / exposed	101 / 211 (47.87%)	66 / 209 (31.58%)	
number of deaths (all causes)	179	186	
number of deaths resulting from adverse events	20	13	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	3 / 211 (1.42%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 211 (1.42%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thromboembolic event			
subjects affected / exposed	3 / 211 (1.42%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death NOS			

subjects affected / exposed	6 / 211 (2.84%)	3 / 209 (1.44%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 6	0 / 3	
Oedema limbs			
subjects affected / exposed	1 / 211 (0.47%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 211 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever			
subjects affected / exposed	2 / 211 (0.95%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 211 (0.47%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 211 (0.47%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pain			
subjects affected / exposed	9 / 211 (4.27%)	3 / 209 (1.44%)	
occurrences causally related to treatment / all	1 / 10	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	9 / 211 (4.27%)	7 / 209 (3.35%)	
occurrences causally related to treatment / all	0 / 9	0 / 7	
deaths causally related to treatment / all	0 / 5	0 / 4	
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed	1 / 211 (0.47%)	0 / 209 (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	2 / 211 (0.95%)	4 / 209 (1.91%)	
occurrences causally related to treatment / all	1 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 211 (0.47%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 211 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 211 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	2 / 211 (0.95%)	2 / 209 (0.96%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	4 / 211 (1.90%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 211 (0.47%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			

subjects affected / exposed	1 / 211 (0.47%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	1 / 211 (0.47%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 211 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
heart failure			
subjects affected / exposed	1 / 211 (0.47%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 211 (0.47%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 211 (0.47%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 211 (0.47%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	3 / 211 (1.42%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Syncope			
subjects affected / exposed	0 / 211 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 211 (0.47%)	2 / 209 (0.96%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	2 / 211 (0.95%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 211 (1.90%)	5 / 209 (2.39%)	
occurrences causally related to treatment / all	0 / 4	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	5 / 211 (2.37%)	4 / 209 (1.91%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
colonic obstruction			
subjects affected / exposed	1 / 211 (0.47%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 211 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	4 / 211 (1.90%)	2 / 209 (0.96%)	
occurrences causally related to treatment / all	5 / 5	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Duodenal stenosis			
subjects affected / exposed	1 / 211 (0.47%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal haemorrhage			
subjects affected / exposed	1 / 211 (0.47%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 211 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 211 (0.47%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 211 (0.47%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal obstruction			
subjects affected / exposed	0 / 211 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal stenosis			
subjects affected / exposed	0 / 211 (0.00%)	3 / 209 (1.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	4 / 211 (1.90%)	8 / 209 (3.83%)	
occurrences causally related to treatment / all	1 / 4	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	2 / 211 (0.95%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			
subjects affected / exposed	0 / 211 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	2 / 211 (0.95%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal perforation			
subjects affected / exposed	1 / 211 (0.47%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomach pain			
subjects affected / exposed	1 / 211 (0.47%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 211 (0.47%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 211 (0.00%)	2 / 209 (0.96%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites and bacterial peritonitis			
subjects affected / exposed	0 / 211 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatobiliary disorders			
Bile duct stenosis			

subjects affected / exposed	0 / 211 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 211 (0.47%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	2 / 211 (0.95%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 211 (1.42%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Haematuria			
subjects affected / exposed	1 / 211 (0.47%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteinuria			
subjects affected / exposed	1 / 211 (0.47%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscle weakness left-sided			
subjects affected / exposed	1 / 211 (0.47%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchial infection			
subjects affected / exposed	1 / 211 (0.47%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Catheter related infection			
subjects affected / exposed	1 / 211 (0.47%)	0 / 209 (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	3 / 211 (1.42%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peritoneal infection			
subjects affected / exposed	1 / 211 (0.47%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sepsis			
subjects affected / exposed	2 / 211 (0.95%)	3 / 209 (1.44%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
Urinary tract infection			
subjects affected / exposed	3 / 211 (1.42%)	2 / 209 (0.96%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
unclear infection			
subjects affected / exposed	1 / 211 (0.47%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 211 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	1 / 211 (0.47%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	2 / 211 (0.95%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 2	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	Safety analysis set Arm A	Safety analysis set Arm B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	211 / 211 (100.00%)	209 / 209 (100.00%)	
Investigations			
Alkaline phosphatase increased			
subjects affected / exposed	11 / 211 (5.21%)	9 / 209 (4.31%)	
occurrences (all)	13	10	
Blood bilirubin increased			
subjects affected / exposed	14 / 211 (6.64%)	15 / 209 (7.18%)	
occurrences (all)	14	19	
Neutrohil count decreased			
subjects affected / exposed	99 / 211 (46.92%)	84 / 209 (40.19%)	
occurrences (all)	174	140	
Platelet count decreased			
subjects affected / exposed	69 / 211 (32.70%)	25 / 209 (11.96%)	
occurrences (all)	115	41	
Weight loss			
subjects affected / exposed	16 / 211 (7.58%)	6 / 209 (2.87%)	
occurrences (all)	19	6	
White blood cell count decreased			
subjects affected / exposed	50 / 211 (23.70%)	44 / 209 (21.05%)	
occurrences (all)	79	62	
Vascular disorders			
Hypertension			
subjects affected / exposed	56 / 211 (26.54%)	12 / 209 (5.74%)	
occurrences (all)	78	12	
Nervous system disorders			
Headache			

subjects affected / exposed	11 / 211 (5.21%)	3 / 209 (1.44%)	
occurrences (all)	12	3	
Peripheral sensory neuropathy			
subjects affected / exposed	10 / 211 (4.74%)	11 / 209 (5.26%)	
occurrences (all)	13	11	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	43 / 211 (20.38%)	59 / 209 (28.23%)	
occurrences (all)	66	68	
General disorders and administration site conditions			
Oedema limbs			
subjects affected / exposed	25 / 211 (11.85%)	9 / 209 (4.31%)	
occurrences (all)	28	9	
Fatigue			
subjects affected / exposed	72 / 211 (34.12%)	62 / 209 (29.67%)	
occurrences (all)	83	68	
Fever			
subjects affected / exposed	14 / 211 (6.64%)	7 / 209 (3.35%)	
occurrences (all)	14	8	
Pain			
subjects affected / exposed	30 / 211 (14.22%)	30 / 209 (14.35%)	
occurrences (all)	36	31	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	30 / 211 (14.22%)	20 / 209 (9.57%)	
occurrences (all)	31	22	
Ascites			
subjects affected / exposed	16 / 211 (7.58%)	7 / 209 (3.35%)	
occurrences (all)	19	7	
Constipation			
subjects affected / exposed	28 / 211 (13.27%)	17 / 209 (8.13%)	
occurrences (all)	28	18	
Diarrhoea			
subjects affected / exposed	55 / 211 (26.07%)	36 / 209 (17.22%)	
occurrences (all)	77	44	
Mucositis oral			

subjects affected / exposed	22 / 211 (10.43%)	13 / 209 (6.22%)	
occurrences (all)	25	13	
Nausea			
subjects affected / exposed	72 / 211 (34.12%)	53 / 209 (25.36%)	
occurrences (all)	98	60	
Vomiting			
subjects affected / exposed	43 / 211 (20.38%)	29 / 209 (13.88%)	
occurrences (all)	57	33	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	26 / 211 (12.32%)	16 / 209 (7.66%)	
occurrences (all)	29	16	
Epistaxis			
subjects affected / exposed	14 / 211 (6.64%)	1 / 209 (0.48%)	
occurrences (all)	15	2	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	29 / 211 (13.74%)	10 / 209 (4.78%)	
occurrences (all)	33	11	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	12 / 211 (5.69%)	7 / 209 (3.35%)	
occurrences (all)	13	7	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	13 / 211 (6.16%)	15 / 209 (7.18%)	
occurrences (all)	15	16	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	23 / 211 (10.90%)	17 / 209 (8.13%)	
occurrences (all)	24	17	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 September 2020	Extansion to phase III study

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported