Clinical trial results:
OPEN, NON CONTROLLED, PARALLEL COHORTS, MULTICENTER, PHASE 2A STUDY FOR THE EVALUATION OF THE ANTITUMOR ACTIVITY OF GM102 SINGLE AGENT AND IN COMBINATION WITH CHEMOTHERAPY IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC COLORECTAL CANCER

Summary

EudraCT number	2018-000627-13
Trial protocol	CZ BE
Global end of trial date	10 February 2021

Results information

Result version number	v1 (current)
This version publication date	02 February 2022
First version publication date	02 February 2022
Summary attachment (see zip file)	C201 Summary of clinical results final (C201-Summary of clinical results from CSR_v1.0_2021-10-18 Final for EudraCT.pdf)

Trial information

Trial identification

Sponsor protocol code	C201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03799731
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GAMAMABS Pharma
Sponsor organisation address	1 Place Pierre Potier, Toulouse, France, 31106
Public contact	Chantal KREZEL, Gamamabs Pharma, 33 184198016, ckrezel@gamamabs.fr
Scientific contact	Jean-François Prost, Gamamabs Pharma, 33 184198016, jfprost@gamamabs.fr

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	02 July 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 February 2021
Global end of trial reached?	Yes
Global end of trial date	10 February 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the anti-tumor activity of GM102 single agent and in combination with trifluridine/tipiracil in locally advanced and metastatic colorectal cancers (CRC).

Protection of trial subjects:

Patients were followed up in dedicated oncology centers through regular visits.
A Trial Steering Committee (TSC) analyzed, qualified murlentamab activity and toxicities and provided recommendations on the IMP (Investigational Medicinal Product, consisting of murlentamab or murlentamab + trifluridine/tipiracil) continuation on a regular basis until study completion.
A careful observation of patients was made from the beginning up to 1 hour after each murlentamab infusion. Blood pressure and heart rate monitoring by a qualified nurse or physician was measured just before and just after murlentamab infusion, so that immediate action can be taken in response to symptoms of an adverse reaction
Concomitant medications should be kept to a minimum during the study , if they are considered as necessary for the patient's welfare and are unlikely to interfere with the IMP, they may be given at the discretion of the investigator:
*Palliative radiotherapy with sponsor, assessment done case by case
*Supportive treatment as medically indicated for the patient’s well-being may be prescribed at the investigator’s discretion

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	04 June 2018
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	Belgium: 40
Country: Number of subjects enrolled	Czechia: 25
Worldwide total number of subjects	65
EEA total number of subjects	65

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)	41
From 65 to 84 years	24
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From Jul-2018 to Mar-2020, 73 patients were screened in the 5 sites participating in the study and 65 (89.0%) patients were enrolled. Overall, 81.8% of the enrolled patients completed 2 cycles (time point for primary endpoint criteria analysis). All patients discontinued the treatment during the study (the main reason was progression).

Pre-assignment

Screening details:

Adult patients with histologically-confirmed metastatic or locally advanced colorectal adenocarcinoma, having failed the previous line of treatment and having received at least two systemic chemotherapy regimens for metastatic colorectal cancer, with at least one of the tumor sites amenable to core needle biopsy; at least one measurable lesion.

Period 1

Period 1 title	Screening period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Arm title	Screening

Arm description:

73 patients were screened for the study and 65 were included as 8 patients did not meet inclusion/ exclusion criteria

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Screening
Started	65
Completed	65

Period 2

Period 2 title	Treatment period
Is this the baseline period?	Yes[1]
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort I

Arm description:

GM102 single agent in refractory patients, having exhausted all therapeutic options. Murlentamab is a humanized glyco-engineered IgG1 antibody targeting AMHRII, administered intravenously over a period of 1 hour at the dose of 7 mg/kg weekly at Days 1, Day 8, Day 15 and Day 21 of each 28-day cycle

Arm type	Experimental
Investigational medicinal product name	Murlentamab
Investigational medicinal product code	GM102
Other name	
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Murlentamab is administered intravenously over a period of 1 hour at the dose of 7 mg/kg weekly at Days 1, Day 8, Day 15 and Day 21 of each 28-day cycle
Murlentamab is diluted in 250 mL NaCl 0.9% polyolefin bags according to the patient weight

Arm title	Cohort II

Arm description:

Murlentamab in combination with trifluridine/tipiracil In patient candidates to receive single agent trifluridine/tipiracil, after at least two lines of treatment for the advanced or metastatic disease.
Murlentamab is administered intravenously over a period of 1 hour at the dose of 7 mg/kg weekly at Days 1, Day 8, Day 15 and Day 21 of each 28-day cycle
Trifluridine/tipiracil is administered orally at the dose of 35mg/m²/dose twice daily on Days 1 to 5 and Days 8 to 12 of each 28-day cycle

Arm type	Experimental
Investigational medicinal product name	Murlentamab
Investigational medicinal product code	GM102
Other name	
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Murlentamab is a humanized glyco-engineered IgG1 antibody targeting AMHRII, administered intravenously over a period of 1 hour at the dose of 7 mg/kg weekly at Days 1, Day 8, Day 15 and Day 21 of each 28-day cycle
The packaging (including perfusion set + unit boxes) is individualised patient-by-patient.
The unit boxes were sent to the centres at 2-8°C with probes in bulk boxes containing the number of unit boxes.
Each murlentamab unit box contains:
- One 20 mL vial containing 150 mg of murlentamab
- Instructions for dilution in Sodium Chloride 0,9%

Each perfusion set (shipped at room temperature) contains: NaCl (NaCl 0.9%) 250 mL bags and tubing.
Murlentamab IS diluted in 250 mL NaCl 0.9% polyolefin bags according to the patient weight

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

Dosage and administration details:

Trifluridine/tipiracil is administered orally at the dose of 35mg/m²/dose twice daily on Days 1 to 5 and Days 8 to 12 of each 28-day cycle (according to patient's body surface area) in combination with murlentamab. Trifluridine/tipiracil is delivered to the patient for one cycle at a time (10 days of treatment each time). The patient returned to the pharmacy unused tablets and empty packs at Day 8 of each cycle and at Day 15 of each cycle for accountability before being given the treatment for the next cycle.
Tablets of 15 mg/6.14 mg or 20/8.19 mg are used in the study

Arm title	Cohort II expansion

Arm description:

Murlentamab in combination with trifluridine/tipiracil in patient candidates to receive single agent trifluridine/tipiracil, after at least two lines of treatment for the advanced or metastatic disease.Murlentamab is administered intravenously over a period of 1 hour at the recommended dose of 7 mg/kg weekly at Days 1, Day 8, Day 15 and Day 21 of each 28-day cycle after a loading dose of 10 mg/kg weekly during 28-day cycle 1.
Trifluridine/tipiracil is administered orally at the dose of 35mg/m²/dose twice daily on Days 1 to 5 and Days 8 to 12 of each 28-day cycle

Arm type	Experimental
Investigational medicinal product name	Murlentamab
Investigational medicinal product code	GM102
Other name	
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Murlentamab is administered intravenously over a period of 1 hour at the dose of 7 mg/kg weekly at Days 1, Day 8, Day 15 and Day 21 of each 28-day cycle after a loading dose of 10 mg/kg weekly during 28-day cycle 1.
Murlentamab is diluted in 250 mL NaCl 0.9% polyolefin bags according to the patient weight

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

Dosage and administration details:

Trifluridine/tipiracil is administered orally at the dose of 35mg/m²/dose twice daily on Days 1 to 5 and Days 8 to 12 of each 28-day cycle (according to patient's body surface area) in combination with murlentamab. Trifluridine/tipiracil is delivered to the patient for one cycle at a time (10 days of treatment each time). The patient returned to the pharmacy unused tablets and empty packs at Day 8 of each cycle and at Day 15 of each cycle for accountability before being given the treatment for the next cycle.
Tablets of 15 mg/6.14 mg or 20/8.19 mg are used in the study

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 has been defined as screening period and is corresponding to the six weeks preceding the first infusion of IMP where all the inclusion/ exclusion criteria were checked.
Baseline is planned at Cycle 1 Day 1 just before the administration of Murlentamab (see the flowchart of the study: appendix 1 of the protocol)

Number of subjects in period 2	Cohort I	Cohort II	Cohort II expansion
Started	21	18	26
Completed	13	13	21
Not completed	8	5	5
Two first cycles not completed	7	4	1
No baseline radiological assessment	-	-	1
No post baseline radiological assessment	1	1	3

Period 3

Period 3 title	Follow-up period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Arm title	Overall safety population

Arm description:

Patients who received at least one dose of IMP. The exact number can't be entered in this item, nevertheless all the patients belonging to the safety population set have a follow-up visit (65 patients)

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 3	Overall safety population
Started	47
Completed	47

Baseline characteristics

Reporting groups	
Reporting group title	Cohort I
Reporting group description:	
GM102 single agent in refractory patients, having exhausted all therapeutic options. Murlentamab is a humanized glyco-engineered IgG1 antibody targeting AMHRII, administered intravenously over a period of 1 hour at the dose of 7 mg/kg weekly at Days 1, Day 8, Day 15 and Day 21 of each 28-day cycle	
Reporting group title	Cohort II
Reporting group description:	
Murlentamab in combination with trifluridine/tipiracil In patient candidates to receive single agent trifluridine/tipiracil, after at least two lines of treatment for the advanced or metastatic disease. Murlentamab is administered intravenously over a period of 1 hour at the dose of 7 mg/kg weekly at Days 1, Day 8, Day 15 and Day 21 of each 28-day cycle Trifluridine/tipiracil is administered orally at the dose of 35mg/m²/dose twice daily on Days 1 to 5 and Days 8 to 12 of each 28-day cycle	
Reporting group title	Cohort II expansion
Reporting group description:	
Murlentamab in combination with trifluridine/tipiracil in patient candidates to receive single agent trifluridine/tipiracil, after at least two lines of treatment for the advanced or metastatic disease.Murlentamab is administered intravenously over a period of 1 hour at the recommended dose of 7 mg/kg weekly at Days 1, Day 8, Day 15 and Day 21 of each 28-day cycle after a loading dose of 10 mg/kg weekly during 28-day cycle 1. Trifluridine/tipiracil is administered orally at the dose of 35mg/m²/dose twice daily on Days 1 to 5 and Days 8 to 12 of each 28-day cycle	

Reporting group values	Cohort I	Cohort II	Cohort II expansion
Number of subjects	21	18	26
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)	11	13	17
From 65-84 years	10	5	9
85 years and over	0	0	0
Age continuous			
The median age was similar between cohorts: approximately 63 in Cohort I, 59 in Initial Cohort II and Cohort II expansion, respectively			
Units: years			
median	63	59	59
inter-quartile range (Q1-Q3)	56 to 70	52 to 66	52 to 66
Gender categorical Units: Subjects			
Female	8	7	12
Male	13	11	14

ECOG performance status Units: Subjects			
Grade 0	6	6	13
Grade 1	15	12	13
CRC primary disease			
Location of the tumor was mainly reported in the colon in the Cohort I and Cohort II expansion: 16 patients (76.2%) and 19 patients (73.1%), respectively. In Initial Cohort II, the location was balanced between colon and rectum			
Units: Subjects			
Colon ascending	3	3	5
Colon descending	1	0	2
Colon hepatic flexure	4	2	2
Colon sigmoid	6	4	9
Colon splenic flexure	1	0	0
Colon transverse	1	0	1
Rectum	5	9	7
Primary tumor differentiation			
Primary tumor was mainly reported as moderately differentiated in all cohorts: 15 patients in Cohort I (75.0%), 10 patients in Cohort II (76.9%) and 15 patients in Cohort II expansion (75.0%), respectively			
Units: Subjects			
Highly differentiated	5	1	1
Low Differentiation Or Undifferentiated Disease	0	2	4
Moderately differentiated	15	10	15
Undetermined	1	5	6
CRC molecular characteristics KRAS			
Mutations when analyzed were mainly reported in KRAS: 13 patients in Cohort I (61.9%), 12 patients in Cohort II (66.7%) and 16 patients in Cohort II expansion (64.0%), respectively			
Units: Subjects			
Not done	0	0	1
If done, mutated	13	12	16
If done, not mutated	8	6	9
Primary surgery			
The majority of the patients benefited from surgery in the time course of their disease (18 patients in Cohort I [85.7%], 15 patients in Initial Cohort II [83.3%] and 22 patients in Cohort II expansion [84.6%], respectively)			
Units: Subjects			
No	3	3	4
Yes	18	15	22
Resection if primary surgery			
Resection was mainly considered as "R0" for most of the patients (n=26, 83.9%) ranging from 62.5% to 100%.			
Units: Subjects			
No resection	3	3	4
If resection, R0	11	5	10
If resection, R1	0	1	0
If resection, R2	0	2	2
If resection, missing value	7	7	10
Time to onset			
Patients included in Initial Cohort II or Cohort II expansion presented mainly synchronous disease when patients included in the Cohort I presented mainly metachronous disease.			
Units: Subjects			
Metachronous disease	13	7	9
Synchronous disease	8	11	17

First location of metastases			
Seven patients (33.3%) of Cohort I, eight patients (44.4%) in Initial Cohort II and eight patients (30.8%) in Cohort II expansion presented at least two metastases. Moreover, one patient (4.8%) in Cohort I, two patients (11.1%) in Initial Cohort II and one patient (3.8%) in Cohort II expansion presented at least three metastasis, respectively. Metastases locations were reported in the liver, peritoneum or in lung, bones, lymph nodes, and ovaries. None of the patients presented brain metastasis			
Units: Subjects			
Liver	13	14	12
Peritoneum	2	1	3
Other	6	3	11
Previous anti-cancer treatment			
All patients had received at least one previous anticancer treatment. Roughly, one half of the patients in the Cohort I (52%) and II expansion (46%) had received at least one previous neoadjuvant and/or adjuvant anti-cancer treatment. The disease at treatment start was mainly located in the colon or rectum in Cohort I (81.8%) and Initial Cohort II (63.6%) when it was mostly metastatic (63.6%) in the Cohort II expansion			
Units: Subjects			
At least 1 prev neoadj and/or adj, local cancer	9	7	4
At least 1 prev neoadj and/or adj, metastat cancer	2	4	7
No previous neoadjuvant and/or adjuvant	10	7	15
Time since diagnosis			
Median time since diagnosis ranged from 2.22 years (Min ; Max: 0.9 ; 7.7) in Cohort II to 3.78 years (Min ; Max: 1.3 ; 9.0) in Cohort I			
Units: Number of years			
median	3.78	2.22	3.02
full range (min-max)	1.3 to 9	0.9 to 7.7	0.9 to 7.9
Time from primary diagnosis to first metastases			
Units: Number of months			
median	2.5	0.13	0.23
full range (min-max)	0 to 43.2	-1.1 to 26.9	-0.5 to 35.4
Time since first metastases			
Units: Number of months			
median	34.07	22.23	30.55
full range (min-max)	11.1 to 100	10.9 to 73.9	10.3 to 80.7
Number of lines of anti cancer treatment			
All patients had received at least one previous metastatic line of treatment. The median number of lines received was higher in Cohort I (4.00, ranged from 1 to 7) as compared to Initial Cohort II and Cohort II expansion that were similar (2.00 vs 2.50, respectively? ranged one to four cohort II and one to six cohort II expansion). Overall, 90.5% (n=19) and 66.7% (n=14) of the patients included in Cohort I, 16.7% (n=3) and 11.1% (n=2) in the Initial Cohort II and 50.0% (n=13) and 30.8% (n=8) of the patients in the Cohort II had received at least three or four lines of metastatic treatment, res			
Units: NUMBER			
median	4	2	2.5
full range (min-max)	2 to 7	1 to 4	1 to 6
Time between last previous anti-cancer treatment and first infusion of murlentamab			
The median time between last previous anti-cancer treatment and first infusion of murlentamab was of 5.29 months (Min ; Max: 2.1 ; 22.1) in Cohort I, 4.44 months (Min ; Max: 2.1 ; 46.7) in Initial Cohort II and 7.54 months (Min ; Max: 2.1 ; 43.4) in Cohort II expansion. The treatment given to the patients in all cohorts included mainly: Fluorouracil, Irinotecan, Oxaliplatin and Bevacizumab			
Units: month			

median	5.29	4.44	7.54
full range (min-max)	2.1 to 22.1	2.1 to 46.7	2.1 to 43.4

Reporting group values	Total		
Number of subjects	65		
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)	41		
From 65-84 years	24		
85 years and over	0		
Age continuous			
The median age was similar between cohorts: approximately 63 in Cohort I, 59 in Initial Cohort II and Cohort II expansion, respectively			
Units: years			
median			
inter-quartile range (Q1-Q3)	-		
Gender categorical			
Units: Subjects			
Female	27		
Male	38		
ECOG performance status			
Units: Subjects			
Grade 0	25		
Grade 1	40		
CRC primary disease			
Location of the tumor was mainly reported in the colon in the Cohort I and Cohort II expansion: 16 patients (76.2%) and 19 patients (73.1%), respectively. In Initial Cohort II, the location was balanced between colon and rectum			
Units: Subjects			
Colon ascending	11		
Colon descending	3		
Colon hepatic flexure	8		
Colon sigmoid	19		
Colon splenic flexure	1		
Colon transverse	2		
Rectum	21		
Primary tumor differentiation			
Primary tumor was mainly reported as moderately differentiated in all cohorts: 15 patients in Cohort I (75.0%), 10 patients in Cohort II (76.9%) and 15 patients in Cohort II expansion (75.0%), respectively			
Units: Subjects			
Highly differentiated	7		
Low Differentiation Or Undifferentiated Disease	6		
Moderately differentiated	40		

Undetermined	12		
CRC molecular characteristics KRAS			
Mutations when analyzed were mainly reported in KRAS: 13 patients in Cohort I (61.9%), 12 patients in Cohort II (66.7%) and 16 patients in Cohort II expansion (64.0%), respectively			
Units: Subjects			
Not done	1		
If done, mutated	41		
If done, not mutated	23		
Primary surgery			
The majority of the patients benefited from surgery in the time course of their disease (18 patients in Cohort I [85.7%], 15 patients in Initial Cohort II [83.3%] and 22 patients in Cohort II expansion [84.6%], respectively)			
Units: Subjects			
No	10		
Yes	55		
Resection if primary surgery			
Resection was mainly considered as "R0" for most of the patients (n=26, 83.9%) ranging from 62.5% to 100%.			
Units: Subjects			
No resection	10		
If resection, R0	26		
If resection, R1	1		
If resection, R2	4		
If resection, missing value	24		
Time to onset			
Patients included in Initial Cohort II or Cohort II expansion presented mainly synchronous disease when patients included in the Cohort I presented mainly metachronous disease.			
Units: Subjects			
Metachronous disease	29		
Synchronous disease	36		
First location of metastases			
Seven patients (33.3%) of Cohort I, eight patients (44.4%) in Initial Cohort II and eight patients (30.8%) in Cohort II expansion presented at least two metastases. Moreover, one patient (4.8%) in Cohort I, two patients (11.1%) in Initial Cohort II and one patient (3.8%) in Cohort II expansion presented at least three metastasis, respectively. Metastases locations were reported in the liver, peritoneum or in lung, bones, lymph nodes, and ovaries. None of the patients presented brain metastasis			
Units: Subjects			
Liver	39		
Peritoneum	6		
Other	20		
Previous anti-cancer treatment			
All patients had received at least one previous anticancer treatment. Roughly, one half of the patients in the Cohort I (52%) and II expansion (46%) had received at least one previous neoadjuvant and/or adjuvant anti-cancer treatment. The disease at treatment start was mainly located in the colon or rectum in Cohort I (81.8%) and Initial Cohort II (63.6%) when it was mostly metastatic (63.6%) in the Cohort II expansion			
Units: Subjects			
At least 1 prev neoadj and/or adj, local cancer	20		
At least 1 prev neoadj and/or adj, metastat cancer	13		
No previous neoadjuvant and/or adjuvant	32		

Time since diagnosis			
Median time since diagnosis ranged from 2.22 years (Min ; Max: 0.9 ; 7.7) in Cohort II to 3.78 years (Min ; Max: 1.3 ; 9.0) in Cohort I			
Units: Number of years median full range (min-max)	- 		
Time from primary diagnosis to first metastases Units: Number of months median full range (min-max)	- 		
Time since first metastases Units: Number of months median full range (min-max)	- 		
Number of lines of anti cancer treatment			
All patients had received at least one previous metastatic line of treatment. The median number of lines received was higher in Cohort I (4.00, ranged from 1 to 7) as compared to Initial Cohort II and Cohort II expansion that were similar (2.00 vs 2.50, respectively? ranged one to four cohort II and one to six cohort II expansion). Overall, 90.5% (n=19) and 66.7% (n=14) of the patients included in Cohort I, 16.7% (n=3) and 11.1% (n=2) in the Initial Cohort II and 50.0% (n=13) and 30.8% (n=8) of the patients in the Cohort II had received at least three or four lines of metastatic treatment, res			
Units: NUMBER median full range (min-max)	- 		
Time between last previous anti-cancer treatment and first infusion of murlentamab			
The median time between last previous anti-cancer treatment and first infusion of murlentamab was of 5.29 months (Min ; Max: 2.1 ; 22.1) in Cohort I, 4.44 months (Min ; Max: 2.1 ; 46.7) in Initial Cohort II and 7.54 months (Min ; Max: 2.1 ; 43.4) in Cohort II expansion. The treatment given to the patients in all cohorts included mainly: Fluorouracil, Irinotecan, Oxaliplatin and Bevacizumab			
Units: month median full range (min-max)	- 		

End points

End points reporting groups

Reporting group title	Screening
Reporting group description:	
73 patients were screened for the study and 65 were included as 8 patients did not meet inclusion/ exclusion criteria	
Reporting group title	Cohort I
Reporting group description:	
GM102 single agent in refractory patients, having exhausted all therapeutic options. Murlentamab is a humanized glyco-engineered IgG1 antibody targeting AMHRII, administered intravenously over a period of 1 hour at the dose of 7 mg/kg weekly at Days 1, Day 8, Day 15 and Day 21 of each 28-day cycle	
Reporting group title	Cohort II
Reporting group description:	
Murlentamab in combination with trifluridine/tipiracil In patient candidates to receive single agent trifluridine/tipiracil, after at least two lines of treatment for the advanced or metastatic disease. Murlentamab is administered intravenously over a period of 1 hour at the dose of 7 mg/kg weekly at Days 1, Day 8, Day 15 and Day 21 of each 28-day cycle Trifluridine/tipiracil is administered orally at the dose of 35mg/m²/dose twice daily on Days 1 to 5 and Days 8 to 12 of each 28-day cycle	
Reporting group title	Cohort II expansion
Reporting group description:	
Murlentamab in combination with trifluridine/tipiracil in patient candidates to receive single agent trifluridine/tipiracil, after at least two lines of treatment for the advanced or metastatic disease.Murlentamab is administered intravenously over a period of 1 hour at the recommended dose of 7 mg/kg weekly at Days 1, Day 8, Day 15 and Day 21 of each 28-day cycle after a loading dose of 10 mg/kg weekly during 28-day cycle 1. Trifluridine/tipiracil is administered orally at the dose of 35mg/m²/dose twice daily on Days 1 to 5 and Days 8 to 12 of each 28-day cycle	
Reporting group title	Overall safety population
Reporting group description:	
Patients who received at least one dose of IMP. The exact number can't be entered in this item, nevertheless all the patients belonging to the safety population set have a follow-up visit (65 patients)	
Subject analysis set title	Cohort I AMHRII<20%
Subject analysis set type	Full analysis
Subject analysis set description:	
AMHRII expression determined by IHC on baseline biopsy Efficacy Evaluable patients	
Subject analysis set title	Cohort I AMHRII≥20%
Subject analysis set type	Full analysis
Subject analysis set description:	
AMHRII expression determined by IHC on baseline biopsy Efficacy Evaluable patients	
Subject analysis set title	Cohort II AMHRII<20%
Subject analysis set type	Full analysis
Subject analysis set description:	
AMHRII expression determined by IHC on baseline biopsy Efficacy Evaluable patients	
Subject analysis set title	Cohort II AMHRII≥20%
Subject analysis set type	Full analysis
Subject analysis set description:	
AMHRII expression determined by IHC on baseline biopsy Efficacy Evaluable patients	
Subject analysis set title	modified Intent To Treat
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The Intention-To Treat (ITT) set is defined as all patients who receive at least one administration of any study drug (murlentamab for Cohort I and murlentamab and/or trifluridine/tipiracil for Cohort II

Subject analysis set title	Efficacy Evaluable set
Subject analysis set type	Full analysis

Subject analysis set description:

Efficacy Evaluable Patient (EEP) set is defined as all ITT patients with radiological baseline assessment and at least one radiological post-baseline assessment and who completed the first two cycles (8 weeks) of treatment

Subject analysis set title	Per Protocol set
Subject analysis set type	Per protocol

Subject analysis set description:

Per Protocol (PP) set consists of all evaluable patients who do not violate the terms of the protocol in a way that would affect the study outcome significantly. All decisions to exclude patients from the PP population were made before locking the database

Subject analysis set title	Pharmacokinetics set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Pharmacokinetics (PK) set is defined as all patients who received at least one dose of any study drug (murlentamab for Cohort I and murlentamab and/or trifluridine/tipiracil for Cohort II), and who had at least one evaluable PK blood sample for murlentamab

Subject analysis set title	Safety set
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety set (SS) was defined for safety analysis: it consists of all patients who receive at least one infusion of murlentamab. Both cohorts were evaluated separately for safety

Primary: Overall Tumor Response Rate (ORR)

End point title	Overall Tumor Response Rate (ORR)[1]

End point description:

Overall Tumor Response Rate (ORR) defined as the proportion of evaluable patients who achieved partial or complete response (RECIST criteria version 1.1) from the end of cycle 2 and subsequently confirmed at least 4 weeks after.
Reporting per arms only for the EEP set.
The co-primary endpoint was not met in Cohort I as no patient achieved either an ORR or a PFS at 6 months.
In the second Cohort overall, the ORR criteria was not met as only one patient achieved a partial response.

End point type	Primary

End point timeframe:

From the end of cycle 2

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: Only descriptive statistics were done in this study: quantitative data summarized by : number of data available, number of missing data, mean, standard deviation, first quartile (Q1), median, third quartile (Q3), minimum and maximum; qualitative data summarized by : number of data available, number of missing data, frequency and percentage for each modality. The percentages were based on the number of data available. All CIs provided computed at 95%; level of significance set at 5% (two-sided)

End point values	Cohort I	Cohort II	Cohort II expansion	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	13	21	
Units: number of patients responders				
number (not applicable)				
investigator assessment Yes	0	0	1	
investigator assessment No	13	13	20	
IRC assessment Yes	0	0	1	
IRC assessment No	13	13	20	

Attachments (see zip file)	ORR and PFS at 6 months /ORR and PFS at 6 months - Primary

Statistical analyses

No statistical analyses for this end point

Primary: Progression free survival (PFS) at 6 months

End point title	Progression free survival (PFS) at 6 months[2]

End point description:

The Progression Free Survival (PFS) at 6 months, defined as the proportion of patients without documented progression or death due to any cause. Reporting per arms only for EEP set
The co-primary endpoint was not met in Cohort I as no patient achieved either an ORR or a PFS at 6 months.
In the second cohort overall, the PFS endpoints was met as 9 out 34 patients were free from progression at 6 months according to Investigators' judgment in the EEP set.

End point type	Primary

End point timeframe:

6 months

Notes:

[2] - 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: Only descriptive statistics were done in this study: quantitative data summarized by : number of data available, number of missing data, mean, standard deviation, first quartile (Q1), median, third quartile (Q3), minimum and maximum; qualitative data summarized by : number of data available, number of missing data, frequency and percentage for each modality. The percentages were based on the number of data available. All CIs provided computed at 95%; level of significance set at 5% (two-sided)

End point values	Cohort I	Cohort II	Cohort II expansion	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	13	21	
Units: number of patients without progression				
number (not applicable)				
investigator assessment Yes	0	4	5	
investigator assessment No	13	9	16	
IRC assessment Yes	0	3	7	
IRC assessment No	13	10	14	

Attachments (see zip file)	ORR and PFS at 6 months /ORR and PFS at 6 months - Primary

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Tumor Response Rate (ORR) iRECIST

End point title	Overall Tumor Response Rate (ORR) iRECIST

End point description:

Immune Objective Response Rate (iORR)
iORR per iRECIST criteria includes the notion of unconfirmed (iUPD) and confirmed progressive disease (iCPD). In case of unconfirmed progression (i.e. IUPD), IMP treatment can be pursued if patient is clinically stable. Patient will be re-assessed at least 4 weeks later and no longer that 8 weeks later for response to treatment (iCR, iPR or iCPD) according to tumor evaluation calculated from baseline tumor target lesions, without taking the previous unconfirmed progression into account.
reporting per cohorts only for EEP set.

End point type	Secondary

End point timeframe:

ORR is also assessed according to iRECIST criteria from the end of cycle 2

End point values	Cohort I	Cohort II	Cohort II expansion	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	13	21	
Units: number of patients responders				
number (not applicable)				
investigator assessment yes	0	0	1	
investigator assessment no	13	13	20	
IRC assessment yes	0	0	1	
IRC assessment no	13	13	20	

Attachments (see zip file)	iORR-Secondary endpoint/immune Objective Response Rate

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical benefit rate (CBR)

End point title	Clinical benefit rate (CBR)

End point description:

Clinical benefit rate (CBR) at each tumor evaluation (number and % of non-progressors, i.e. CR+PR+SD) using RECIST and iRECIST criteria. Proportion of patients who are non-progressors (radiologically and clinically, including responders and stabilized patients, using RECIST 1.1 and iRECIST criteria) from the first administration of murlentamab (cohort I) or murlentamab + trifluridine/tipiracil (Cohort II) at 8 (+/- 10 days, end of cycle 2) and 16 (+/- 15 days, end of cycle 4) weeks.
Overall, only one patient in Cohort II expansion achieved a partial response . In addition, patients in Cohort II overall were more likely to achieve a stable disease than patient included in Cohort I: five patients (38.5%) in Cohort I, nine patients (69.2%) in Cohort II and 15 patients (71.4%) in Cohort II expansion, respectively.

End point type	Secondary

End point timeframe:

End of cycle 2: 8 weeks and end of cycle 4 (16 weeks)

End point values	Cohort I	Cohort II	Cohort II expansion	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	13	21	
Units: number of patients non progressors				
number (not applicable)				
at 8 weeks yes	0	2	0	
at 8 weeks no	13	11	21	
at 16 weeks yes	0	2	0	
at 16 weeks no	13	11	21	

Attachments (see zip file)	CBR- Secondary endpoint/Clinical Benefit Rate (CBR) -

Statistical analyses

No statistical analyses for this end point

Secondary: Tumor Growth Rate (TGR)

End point title	Tumor Growth Rate (TGR)

End point description:

Tumor Growth Rate (TGR) pre and under treatment (at the first tumor evaluation under treatment).TGR curves (pretreatment and after completion of 2 cycles, at the first on-treatment CT scan) was calculated and displayed for each patient.
Tumor growth rate was evaluable in the EEP set in the majority of the patient of the Cohort I and Cohort II (11 patients, 84.6% in both cohorts). On the contrary, TGR evaluation was only available in six patients (28.6%) of the Cohort II expansion which limits the impact of the analysis in this cohort. Nevertheless, among these patients, all but three patients included in Cohort II (patients 04-05, 01-06 and 02-01) and two patients included in Cohort I (patients 01-03 and 01-11) reported a negative percentage of variation in the TGR.

End point type	Secondary

End point timeframe:

End of cycle 2 (8 weeks)

End point values	Cohort I	Cohort II	Cohort II expansion	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	10	6	
Units: percent				
median (full range (min-max))	-33.19 (-122 to 118.2)	-58.76 (-224.8 to 744.6)	-101.7 (-108.3 to -11.9)	

Attachments (see zip file)	TGR-Secondary endpoint/Tumor Growth Rate (TGR)-Secondary

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (PFS)

End point title	Progression free survival (PFS)

End point description:

PFS is defined (proportion of patients) as the time elapsed from the date of 1st infusion to the date of documented progression or death due to any cause, whichever occurs first. Patients without documented progression are censored at the date of last response assessment that is stable disease or better. After 2 months, only 1 patient (7.7%), 6 patients (46.2%) and 11 patients (52.4%) are still considered as non-progressors in the Cohort I, Cohort II and II expansion, respectively. After 10 months, 1 patient (7.7%) and 2 patients (9.5%) are still at risk in Cohort II and II expansion, respectively. When considering AMHRII membrane expression, no modification was observed in Cohort I while in Cohort II overall patients presenting AMHRII membrane expression ≥20% presented a higher PFS than those with AMHRII membrane expression <20% according to RECIST criteria with median [95% CI] PFS of 1.77 months [1.71 - 1.87] vs 3.55 months [2.04 - 6.90], respectively

End point type	Secondary

End point timeframe:

Up to the progression date

End point values	Cohort I AMHRII<20%	Cohort I AMHRII≥20%	Cohort II AMHRII<20%	Cohort II AMHRII≥20%
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	3	17	13
Units: number of patients who progressed				
number (not applicable)				
At 2 months	6	3	14	2
At 4 months	6	3	15	9
At 6 months	6	3	15	9
At 8 months	6	3	17	11
At 10 months	6	3	17	11
At 12 months	6	3	17	13
At 14 months	6	3	17	13

Attachments (see zip file)	PFS-secondary endpoint/Progression Free Survival (PFS) -

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is defined as the time elapsed from the date of first infusion to the date of death whatever the cause. OS will be primarily analyzed on the ITT set. Patients without documentation of death at the time of analysis will be censored at the date last known to be alive. By the time of the analysis, after 36 months follow-up for the EEP, all patients (100%) in the Cohort I, 92.3% patients in initial Cohort II (12 events, 1 censor), and 71.4% of the patients of Cohort II expansion (15 events, 6 censors) had died. When considering AMHRII membrane expression, patients in Cohort II with expression ≥20% tended to have a longer OS than those with an AMHRII expression <20% with a Median [95% CI] OS of 9.00 months [3.68 - 11.47] vs 11.76 months [7.13 - 22.37], respectively (p-value for Logrank test is 0.2129). On the contrary, the loading dose in Cohort II overall did not show any impact on OS (p-value for Logrank test is 0.4345).

End point type	Secondary

End point timeframe:

Up to the death or the analysis cut-off date

End point values	Cohort I AMHRII<20%	Cohort I AMHRII≥20%	Cohort II AMHRII<20%	Cohort II AMHRII≥20%
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	3	17	13
Units: number of dead patients				
number (not applicable)				
at 2 months	0	0	0	0
at 4 months	2	0	5	0
at 6 months	3	2	6	2
at 8 months	4	2	7	4
at 10 months	4	3	9	5
at 12 months	5	3	13	7
at 14 months	5	3	13	9
at 16 months	5	3	13	9
at 18 months	5	3	13	9
at 20 months	5	3	13	9
at 22 months	6	3	14	9
at 24 months	6	3	14	10
at 26 months	6	3	14	10
at 28 months	6	3	14	10
at 30 months	6	3	14	10
at 32 months	6	3	14	10

at 34 months	6	3	14	10
at 36 months	6	3	14	10

Attachments (see zip file)	OS-Secondary endpoint/Overall Survival (OS) - Secondary

Statistical analyses

No statistical analyses for this end point

Secondary: PD evaluation: AMHRII expression

End point title	PD evaluation: AMHRII expression

End point description:

AMHRII expression by immunostaining (IHC) in archived tumor samples, in the baseline biopsies and in the biopsy performed under murlentamab treatment (after 2 cycles of treatment). AMHRII expression at the tumor cell membrane from patient biopsies was evaluated by Institut Curie before (screening visit) and under treatment (at the end of Cycle 2) and presented in a specific report enclosed ro CSR. Moreover, a listing summarizing AMHRII expression in tumor cells at the cell membrane pre and under treatment for each patient is presented. AMHRII expression determined by IHC on baseline biopsy was available for 16 patients (76.2%) in Cohort I, 18 patients (100%) in Cohort II and 22 patients (84.6%) in Cohort II expansion, respectively. AMHRII membrane expression was ≥20% in four (25.0%) patients in cohort I, seven (38.9%) patients in Initial Cohort II and nine (40.9%) patients in cohort II expansion, respectively

End point type	Secondary

End point timeframe:

Up to the end of cycle 2

End point values	Cohort I	Cohort II	Cohort II expansion	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	13	17	
Units: Number of patients				
number (not applicable)				
Baseline AMHRII<20%	6	8	9	
Baseline AMHRII≥20%	3	5	8	

Statistical analyses

No statistical analyses for this end point

Secondary: Exposure to murlentamab

End point title	Exposure to murlentamab

End point description:

Pharmacokinetic analysis of murlentamab was performed by Eurofins ADME (report enclosed to CSR) on the pharmacokinetics set by cohort (Cohort I, Cohort II, Cohort II expansion, Cohort II overall) and by loading dose (7mg/kg and 10mg/kg) within Cohort II overall. Descriptive statistics (individual data listing of serum concentration) of murlentamab serum concentration (µg/mL) at Day 1 and Day 15 of

the first 2 cycles and at end of treatment visit when available, before infusion and 1 hour after the start of murlentamab infusion.

End point type	Secondary

End point timeframe:

Day 1 and Day 15 of the first 2 cycles and at end of treatment (EOT) visit (7 days after the last IMP infusion) when available

End point values	Cohort I	Cohort II	Cohort II expansion	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	18	26	
Units: Number of patients				
number (not applicable)				
Treatment compliance between 90-110% yes	21	17	22	
Treatment compliance between 90-110% no	0	1	4	

Attachments (see zip file)	Exposure of Murlentamab/Exposure to Murlentamab -

Statistical analyses

No statistical analyses for this end point

Secondary: Exposure of patients to trifluridine in cohort II

End point title	Exposure of patients to trifluridine in cohort II[3]

End point description:

Exposure of patients to trifluridine in cohort II will be assessed through description of trifluridine plasma concentrations in PK samples in the first 18 patients enrolled in cohort II. Pharmacokinetics' analysis report was done by Eurofins ADME BIOANALYSES and report is enclosed to CSR. Trifluridine/tipiracil exposure (only for Cohort II) was calculated and analyzed by an external company (Eurofins ADME BIOANALYSES).
Descriptive statistics (individual data listing of trifluridine/tipiracil plasma concentration (ng/mL)) at Day 1 and Day 15 of the first 2 cycles and at end of treatment visit when available, before infusion and 1 hour after the start of murlentamab infusion.

End point type	Secondary

End point timeframe:

Day 1 and Day 15 of the first 2 cycles and at end of treatment (EOT) visit (7 days after the last IMP administration) when available

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Trifluridine was administered (trifluridine/tipiracil) in combination with Murlentamab in the cohorts II and II expansion. It was decided to measure the concentration of trifluridine only in the cohort II;

End point values	Cohort II			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: concentration				
arithmetic mean (standard deviation)				
Cycle 1 Day 15	137.92 (± 552.01)			
Cycle 2 Day 1	0.28591 (± 1.1788)			
Cycle 2 Day 15	3.4481 (± 4.059)			
End of Treatment (EoT)	5.5751 (± 15.769)			

Attachments (see zip file)	Exposure to Trifluridine/Exposure to Trifluridine (only cohort II)

Statistical analyses

No statistical analyses for this end point

Secondary: Evidence of anti-murlentamab antibodies (ADA)

End point title	Evidence of anti-murlentamab antibodies (ADA)

End point description:

Evidence of anti-murlentamab antibodies (ADA) at screening, at the beginning of every even cycle (pre-dose), and at the end of treatment visit.Anti-murlentamab antibodies results (Positive / Negative) will be described at Screening visit, at Day 1 of each performed cycle and at end of treatment. At screening, one patient (4.8%) in Cohort I, two patients (11.1%) Cohort II and one patient (3.8%) Cohort II expansion presented anti-murlentamab antibodies at screening. Subsequently, anti-murlentamab antibodies were only found in the same patient of the Cohort II expansion until C10D1. At the end of treatment, anti-murlentamab antibodies were found in one patient in Cohort II (7.7%) and one patient in Cohort II expansion (5.3%); these patients presented already these ADAs at screening.

End point type	Secondary

End point timeframe:

At screening, beginning of even cycles and at the end of study

End point values	Cohort I	Cohort II	Cohort II expansion	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	18	26	
Units: number of positive or negative				
number (not applicable)				
Screening negative	20	16	25	
Screening positive	1	2	1	
C2D1 negative	17	16	22	
C2D1 positive	0	0	1	
End of treatment negative	16	12	18	
End of treatment positive	0	1	1	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time informed consent is signed until at least 30 days after the last IMP administration. Safety evaluation is performed on safety set and by cohort.

Adverse event reporting additional description:

Type, frequency, seriousness, severity and relatedness of IMP emergent adverse events (TEAEs) analyzed. 923 AEs were recorded for 64 patients (98.5%). Only the number of patients affected is reported. None SAE related to GM102. The general health deterioration resulting in death in cohort I is related to disease progression and not to murlentamab

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Cohort I

Reporting group description:

Cohort I (GM102 single agent) in refractory patients, having exhausted all therapeutic options; monotherapy, with 15 evaluable patients for efficacy. Murlentamab administered at the recommended dose of 7 mg/kg weekly

Reporting group title	Cohort II

Reporting group description:

Cohort II (murlentamab in combination with trifluridine/tipiracil) in patient candidates to receive single agent trifluridine/tipiracil, after at least two lines of treatment for the advanced or metastatic disease. Cohort II: combination, with 35-40 evaluable patients for efficacy (cohort II and cohort expansion) The first 18 patients (cohort II) received murlentamab at the recommended dose of 7 mg/kg weekly combined with trifluridine/tipiracil at the dose of 35 mg/m2/dose administered orally twice daily on Days 1 to 5 and Days 8 to 12 of each 28-day cycle

Reporting group title	Cohort II expansion

Reporting group description:

Cohort II (murlentamab in combination with trifluridine/tipiracil) in patient candidates to receive single agent trifluridine/tipiracil, after at least two lines of treatment for the advanced or metastatic disease. Cohort II: combination, with 35-40 evaluable patients for efficacy (cohort II and cohort expansion) The additional 25 patients (cohort II expansion)will receive the recommended murlentamab loading dose of 10 mg/kg q1w during the first 28-day cycle combined with trifluridine/tipiracil at the dose of 35 mg/m2/dose administered orally twice daily on Days 1 to 5 and Days 8 to 12. The objective is to reach murlentamab steady state during the first 28-day cycle. During the subsequent 28-day cycles, murlentamab will be administered at the recommended dose of 7 mg/kg weekly, combined with trifluridine/tipiracil at the dose of 35 mg/m2/dose administered orally twice daily on Days 1 to 5 and Days 8 to 12 of each 28-day cycle.

Serious adverse events	Cohort I	Cohort II	Cohort II expansion
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 21 (28.57%)	5 / 18 (27.78%)	4 / 26 (15.38%)
number of deaths (all causes)	9	7	11
number of deaths resulting from adverse events	1	0	0
Nervous system disorders			
Cerebral ischaemia	Additional description: Not related to IMP but to underlying disease		

subjects affected / exposed	1 / 21 (4.76%)	0 / 18 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia	Additional description: Not related to IMP but to underlying disease		
subjects affected / exposed	1 / 21 (4.76%)	0 / 18 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration	Additional description: Patient 01-05 SAE"General deterioration" (abdominal pain) leading to the patient's hospitalization from 27-Sep-2018 to 12-Oct-2018 and then to the patient's death on 30-Oct-2018. SAE not related to the IMPs, but related to the underlying disease.		
subjects affected / exposed	1 / 21 (4.76%)	0 / 18 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Blood and lymphatic system disorders			
Neutropenia	Additional description: related to trifluridine/tipiracil		
subjects affected / exposed	0 / 21 (0.00%)	5 / 18 (27.78%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	5 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia	Additional description: related to trifluridine/tipiracil		
subjects affected / exposed	0 / 21 (0.00%)	1 / 18 (5.56%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation	Additional description: Not related to IMP but to underlying disease		
subjects affected / exposed	1 / 21 (4.76%)	0 / 18 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction	Additional description: One of this event led to trifluridine/tipiracil discontinuation for the patient affected in cohort II expansion. Not related to IMP but to underlying disease		
subjects affected / exposed	0 / 21 (0.00%)	1 / 18 (5.56%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia, obstructive	Additional description: Not related to IMP but to underlying disease		

subjects affected / exposed	0 / 21 (0.00%)	1 / 18 (5.56%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism	Additional description: Not related to IMP but to underlying disease		
subjects affected / exposed	1 / 21 (4.76%)	0 / 18 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	0 / 21 (0.00%)	0 / 18 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis	Additional description: Not related to IMP but to underlying disease		
subjects affected / exposed	1 / 21 (4.76%)	0 / 18 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infection	Additional description: Not related to IMP but to underlying disease		
subjects affected / exposed	1 / 21 (4.76%)	0 / 18 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia	Additional description: Not related to IMP but to underlying disease		
subjects affected / exposed	1 / 21 (4.76%)	0 / 18 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection	Additional description: Not related to IMP but to underlying disease		
subjects affected / exposed	0 / 21 (0.00%)	0 / 18 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypomagnesaemia	Additional description: Not related to IMP but to underlying disease		

subjects affected / exposed	0 / 21 (0.00%)	0 / 18 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Cohort I	Cohort II	Cohort II expansion
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 21 (100.00%)	18 / 18 (100.00%)	25 / 26 (96.15%)
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	0 / 21 (0.00%)	1 / 18 (5.56%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 21 (28.57%)	4 / 18 (22.22%)	14 / 26 (53.85%)
occurrences (all)	6	4	14
Pyrexia			
subjects affected / exposed	7 / 21 (33.33%)	0 / 18 (0.00%)	3 / 26 (11.54%)
occurrences (all)	7	0	3
Oedema peripheral			
subjects affected / exposed	4 / 21 (19.05%)	3 / 18 (16.67%)	2 / 26 (7.69%)
occurrences (all)	4	3	2
Asthenia			
subjects affected / exposed	5 / 21 (23.81%)	2 / 18 (11.11%)	1 / 26 (3.85%)
occurrences (all)	5	2	1
Mucosal inflammation			
subjects affected / exposed	0 / 21 (0.00%)	0 / 18 (0.00%)	4 / 26 (15.38%)
occurrences (all)	0	0	4
Chest pain			
subjects affected / exposed	1 / 21 (4.76%)	1 / 18 (5.56%)	1 / 26 (3.85%)
occurrences (all)	1	1	1
General physical health deterioration			
subjects affected / exposed	1 / 21 (4.76%)	1 / 18 (5.56%)	0 / 26 (0.00%)
occurrences (all)	1	1	0
Reproductive system and breast			

disorders			
Pelvic pain			
subjects affected / exposed	0 / 21 (0.00%)	1 / 18 (5.56%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 21 (14.29%)	2 / 18 (11.11%)	5 / 26 (19.23%)
occurrences (all)	3	2	5
Cough			
subjects affected / exposed	3 / 21 (14.29%)	3 / 18 (16.67%)	3 / 26 (11.54%)
occurrences (all)	3	3	3
Epistaxis	Additional description: Observed only in the groups murlentamab+trifluridine/tipiracil		
subjects affected / exposed	0 / 21 (0.00%)	1 / 18 (5.56%)	1 / 26 (3.85%)
occurrences (all)	0	1	1
Oropharyngeal pain			
subjects affected / exposed	0 / 21 (0.00%)	2 / 18 (11.11%)	0 / 26 (0.00%)
occurrences (all)	0	2	0
Rhinorrhoea			
subjects affected / exposed	0 / 21 (0.00%)	0 / 18 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	2
Dry throat			
subjects affected / exposed	0 / 21 (0.00%)	1 / 18 (5.56%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Rales			
subjects affected / exposed	0 / 21 (0.00%)	0 / 18 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 21 (9.52%)	1 / 18 (5.56%)	3 / 26 (11.54%)
occurrences (all)	2	1	3
Confusional state			
subjects affected / exposed	0 / 21 (0.00%)	1 / 18 (5.56%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Investigations			
White blood cell count decreased	Additional description: Observed only in the groups murlentamab+trifluridine/tipiracil		

subjects affected / exposed	0 / 21 (0.00%)	2 / 18 (11.11%)	7 / 26 (26.92%)
occurrences (all)	0	2	7
Blood bilirubin increased			
subjects affected / exposed	3 / 21 (14.29%)	3 / 18 (16.67%)	2 / 26 (7.69%)
occurrences (all)	3	3	2
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 21 (4.76%)	1 / 18 (5.56%)	5 / 26 (19.23%)
occurrences (all)	1	1	5
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 21 (4.76%)	2 / 18 (11.11%)	2 / 26 (7.69%)
occurrences (all)	1	2	2
Alanine aminotransferase increased	Additional description: Observed only in the groups murlentamab+trifluridine/tipiracil		
subjects affected / exposed	0 / 21 (0.00%)	2 / 18 (11.11%)	2 / 26 (7.69%)
occurrences (all)	0	2	2
Neutrophil count decreased	Additional description: Observed only in the groups murlentamab+trifluridine/tipiracil		
subjects affected / exposed	0 / 21 (0.00%)	1 / 18 (5.56%)	2 / 26 (7.69%)
occurrences (all)	0	1	2
Weight decreased			
subjects affected / exposed	1 / 21 (4.76%)	1 / 18 (5.56%)	1 / 26 (3.85%)
occurrences (all)	1	1	1
Blood creatinine increased	Additional description: Observed only in the groups murlentamab+trifluridine/tipiracil		
subjects affected / exposed	0 / 21 (0.00%)	1 / 18 (5.56%)	1 / 26 (3.85%)
occurrences (all)	0	1	1
Body temperature increased			
subjects affected / exposed	0 / 21 (0.00%)	1 / 18 (5.56%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 21 (4.76%)	2 / 18 (11.11%)	0 / 26 (0.00%)
occurrences (all)	1	2	0
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	1 / 21 (4.76%)	3 / 18 (16.67%)	3 / 26 (11.54%)
occurrences (all)	1	3	3
Headache			

subjects affected / exposed	1 / 21 (4.76%)	1 / 18 (5.56%)	3 / 26 (11.54%)
occurrences (all)	1	1	3
Dizziness			
subjects affected / exposed	1 / 21 (4.76%)	2 / 18 (11.11%)	0 / 26 (0.00%)
occurrences (all)	1	2	0
Burning sensation			
subjects affected / exposed	0 / 21 (0.00%)	1 / 18 (5.56%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 21 (0.00%)	1 / 18 (5.56%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 21 (23.81%)	11 / 18 (61.11%)	14 / 26 (53.85%)
occurrences (all)	5	11	14
Neutropenia	Additional description: Observed only in the groups murlentamab+trifluridine/tipiracil		
subjects affected / exposed	0 / 21 (0.00%)	12 / 18 (66.67%)	18 / 26 (69.23%)
occurrences (all)	0	12	18
Thrombocytopenia	Additional description: Observed only in the groups murlentamab+trifluridine/tipiracil		
subjects affected / exposed	0 / 21 (0.00%)	5 / 18 (27.78%)	4 / 26 (15.38%)
occurrences (all)	0	5	4
Leukopenia	Additional description: Observed only in the groups murlentamab+trifluridine/tipiracil		
subjects affected / exposed	0 / 21 (0.00%)	3 / 18 (16.67%)	1 / 26 (3.85%)
occurrences (all)	0	3	1
Febrile neutropenia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 18 (5.56%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Vertigo	Additional description: Observed only in the groups murlentamab+trifluridine/tipiracil		
subjects affected / exposed	0 / 21 (0.00%)	1 / 18 (5.56%)	2 / 26 (7.69%)
occurrences (all)	0	1	2
Eye disorders			
Lacrimation increased	Additional description: Observed only in the groups murlentamab+trifluridine/tipiracil		
subjects affected / exposed	0 / 21 (0.00%)	1 / 18 (5.56%)	1 / 26 (3.85%)
occurrences (all)	0	1	1

Gastrointestinal disorders			
Nausea			
subjects affected / exposed	5 / 21 (23.81%)	12 / 18 (66.67%)	9 / 26 (34.62%)
occurrences (all)	5	12	9
Abdominal pain			
subjects affected / exposed	6 / 21 (28.57%)	8 / 18 (44.44%)	6 / 26 (23.08%)
occurrences (all)	6	8	6
Constipation			
subjects affected / exposed	6 / 21 (28.57%)	3 / 18 (16.67%)	8 / 26 (30.77%)
occurrences (all)	6	3	8
Diarrhoea	Additional description: Observed only in the groups murlentamab+trifluridine/tipiracil		
subjects affected / exposed	0 / 21 (0.00%)	5 / 18 (27.78%)	11 / 26 (42.31%)
occurrences (all)	0	5	11
Vomiting			
subjects affected / exposed	3 / 21 (14.29%)	5 / 18 (27.78%)	7 / 26 (26.92%)
occurrences (all)	3	5	7
Stomatitis			
subjects affected / exposed	1 / 21 (4.76%)	3 / 18 (16.67%)	2 / 26 (7.69%)
occurrences (all)	1	3	2
Abdominal pain upper			
subjects affected / exposed	2 / 21 (9.52%)	2 / 18 (11.11%)	1 / 26 (3.85%)
occurrences (all)	2	2	1
Ascites			
subjects affected / exposed	1 / 21 (4.76%)	2 / 18 (11.11%)	0 / 26 (0.00%)
occurrences (all)	1	2	0
Flatulence			
subjects affected / exposed	1 / 21 (4.76%)	0 / 18 (0.00%)	2 / 26 (7.69%)
occurrences (all)	1	0	2
Proctalgia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 18 (5.56%)	2 / 26 (7.69%)
occurrences (all)	0	1	2
Small intestinal obstruction	Additional description: Observed only in the groups murlentamab+trifluridine/tipiracil		
subjects affected / exposed	0 / 21 (0.00%)	1 / 18 (5.56%)	2 / 26 (7.69%)
occurrences (all)	0	1	2
Gingival erosion			

subjects affected / exposed	1 / 21 (4.76%)	1 / 18 (5.56%)	0 / 26 (0.00%)
occurrences (all)	1	1	0
Abdominal pain lower			
subjects affected / exposed	0 / 21 (0.00%)	1 / 18 (5.56%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Aerophagia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 18 (5.56%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Anal haemorrhage			
subjects affected / exposed	0 / 21 (0.00%)	1 / 18 (5.56%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Gingival bleeding			
subjects affected / exposed	0 / 21 (0.00%)	1 / 18 (5.56%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Umbilical hernia, obstructive			
subjects affected / exposed	0 / 21 (0.00%)	1 / 18 (5.56%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 18 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	2
Ocular icterus			
subjects affected / exposed	2 / 21 (9.52%)	0 / 18 (0.00%)	0 / 26 (0.00%)
occurrences (all)	2	0	0
Hepatic cytolysis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 18 (5.56%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Hepatic pain			
subjects affected / exposed	0 / 21 (0.00%)	1 / 18 (5.56%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Cholangitis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 18 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Alopecia	Additional description: Observed only in the groups murlentamab+trifluridine/tipiracil		

subjects affected / exposed	0 / 21 (0.00%)	3 / 18 (16.67%)	2 / 26 (7.69%)
occurrences (all)	0	3	2
Pruritus	Additional description: Observed only in the groups murlentamab+trifluridine/tipiracil		
subjects affected / exposed	0 / 21 (0.00%)	1 / 18 (5.56%)	1 / 26 (3.85%)
occurrences (all)	0	1	1
Skin toxicity			
subjects affected / exposed	0 / 21 (0.00%)	1 / 18 (5.56%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	0 / 21 (0.00%)	1 / 18 (5.56%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 21 (9.52%)	2 / 18 (11.11%)	3 / 26 (11.54%)
occurrences (all)	2	2	3
Back pain			
subjects affected / exposed	4 / 21 (19.05%)	1 / 18 (5.56%)	2 / 26 (7.69%)
occurrences (all)	4	1	2
Pain in extremity	Additional description: Observed only in the groups murlentamab+trifluridine/tipiracil		
subjects affected / exposed	0 / 21 (0.00%)	1 / 18 (5.56%)	2 / 26 (7.69%)
occurrences (all)	0	1	2
Muscle spasms			
subjects affected / exposed	0 / 21 (0.00%)	0 / 18 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	2
Neck pain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 18 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	2
Flank pain			
subjects affected / exposed	0 / 21 (0.00%)	1 / 18 (5.56%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Infection			
subjects affected / exposed	2 / 21 (9.52%)	0 / 18 (0.00%)	0 / 26 (0.00%)
occurrences (all)	2	0	0
Nasopharyngitis			

subjects affected / exposed	1 / 21 (4.76%)	1 / 18 (5.56%)	0 / 26 (0.00%)
occurrences (all)	1	1	0
Tooth infection			
subjects affected / exposed	0 / 21 (0.00%)	1 / 18 (5.56%)	1 / 26 (3.85%)
occurrences (all)	0	1	1
Urinary tract infection			
subjects affected / exposed	0 / 21 (0.00%)	0 / 18 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	2
Bacterial vaginosis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 18 (5.56%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal gonococcal infection			
subjects affected / exposed	0 / 21 (0.00%)	1 / 18 (5.56%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Tooth abscess			
subjects affected / exposed	0 / 21 (0.00%)	1 / 18 (5.56%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 21 (23.81%)	8 / 18 (44.44%)	10 / 26 (38.46%)
occurrences (all)	5	8	10
Hypokalaemia			
subjects affected / exposed	2 / 21 (9.52%)	3 / 18 (16.67%)	4 / 26 (15.38%)
occurrences (all)	2	3	4
Hypocalcaemia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 18 (0.00%)	3 / 26 (11.54%)
occurrences (all)	0	0	3
Hypomagnesaemia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 18 (0.00%)	3 / 26 (11.54%)
occurrences (all)	0	0	3
Hypoproteinaemia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 18 (0.00%)	3 / 26 (11.54%)
occurrences (all)	0	0	3
Vitamin D deficiency			
subjects affected / exposed	0 / 21 (0.00%)	0 / 18 (0.00%)	3 / 26 (11.54%)
occurrences (all)	0	0	3

Dehydration			
subjects affected / exposed	1 / 21 (4.76%)	1 / 18 (5.56%)	0 / 26 (0.00%)
occurrences (all)	1	1	0
Hyperglycaemia	Additional description: Observed only in the groups murlentamab+trifluridine/tipiracil		
subjects affected / exposed	0 / 21 (0.00%)	1 / 18 (5.56%)	1 / 26 (3.85%)
occurrences (all)	0	1	1
Hyperuricaemia			
subjects affected / exposed	1 / 21 (4.76%)	1 / 18 (5.56%)	0 / 26 (0.00%)
occurrences (all)	1	1	0
Hyponatraemia			
subjects affected / exposed	1 / 21 (4.76%)	1 / 18 (5.56%)	0 / 26 (0.00%)
occurrences (all)	1	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 June 2018	Addition of regorafenib in the available therapies for which pateints of cohort II are not considered for (see inclusion criterion 8 below): "Cohort II (combination with trifluridine/tipiracil): patients eligible for trifluridine/tipiracil who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, regorafenib and anti-EGFR agents. Patients must have received at least 2 prior lines of standard chemotherapy for mCRC". Addition of an exclusion criterion: 12. Severe New York Heart Association (NYHA) III and IV heart failure Suppression of to a hospital for the patient deprived of liberty in exclusion criterion 15 "Patient deprived of liberty by a judicial or administrative decision, patient admitted to a hospital, social institution or who is under a measure of legal protection, patient hospitalized without consent or who is in an emergency situation." Increase of monitoring duration after the first infusion of GM102 to 2 hours: "Patients must be closely monitored during infusions of GM102, during two hours at least after the end of the first infusion and then during one hour at least after the end of subsequent infusions. Blood pressure and heart rate monitoring by a qualified nurse or physician should be measured just before and just after GM102 infusion, so that immediate action can be taken in response to symptoms of an adverse reaction" Protocol amended with this first amendment is Protocol version v2.0 of 15-May-2018
03 December 2019	Protocol C201 was amended to version 3.0 to increase the sample size of cohort II to 25 additional patients to be enrolled, with the objective to obtain at least 35 evaluable patients in cohort II to gather more information on the efficacy of murlentamab plus trifluridine/tipiracil in metastatic pretreated CRC patients. More data on AMHRII expression on tumor cells at baseline and under treatment will be obtained aiming at determining an IHC assay for future trials for patient selection and future analytical validation. First preliminary results of the study on the 39 patients analyzed in both cohorts (cut-off date of April 24, 2019), suggested a longer than expected PFS for murlentamab + trifluridine/tipiracil, especially for patients with marked AMHRII expression. A larger cohort of patients treated with the combination will allow to investigate a potential relationship between the level of AMHRII expression in tumoral cells, the clinical response to treatment and the patient overall outcome (progression-free survival becoming a primary endpoint and overall survival). The hypothesis to demonstrate: 85% of probability that the true number of patients free of progression at 6 months is greater than 15% if 8 out of 35 patients (~30%) are free of progression for trifluridine/tipiracil single agent In addition, the PFS at 6 months was moved from secondary to primary endpoint, an exploratory endpoint was added to investigate the potential relationship between AMHRII IHC expression and response to treatment and patient overall outcome, an exclusion criterion has been added to exclude patients with known allergy to rodents as Murlentamab is produced from a rat myeloma cell line (YB2/0); archived tumoral tissue is available and collected to assess AMHRII expression, relevant biomarkers and tumor microenvironment features at an earlier stage of the disease, in addition to the baseline and under treatment tumor biopsy. Protocol version v3.0 of 06-November-2019

28 April 2020	Protocol C201, version 3.0 from 6 November 2019,was amended to a version 4.0 in the context of the Covid-19 pandemic and in accordance to the related EMA Guidance (Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic, Version 1 (20/03/2020)) .The objectives of this amendment are to ensure as a priority the health and safety of trial participants, to allow them to remain in the trial as long they have a benefit, and to preserve the validity of data in order to reach the trial objectives."Substantial amendment" on safety measures related to Covid-19 pandemic with an immediate implementation on all sites as agreed with the study coordinating investigator and the principal investigator of each site.In addition, the principal investigator of each site has to conduct a Covid-19 risk assessment for each patient under study drug in the C201 expansion study, as recommended by the EMA guidance. Recruitment put on hold since 26 patients have been included so far.Patients withdrawn for Covid-19 will be replaced (as we can't assess the PFS for these patients); recruitment will restart to replace non evaluable patients or patients withdrawn for Covid-19;an exclusion criterion is added: "Patient positive to Covid 19". If it is not possible to collect the tumoral biopsy at the end of cycle 2, it must be done at the end of cycle 3 or end of cycle 4 or at the end of treatment in case of premature termination whatever the reason; the biopsy under treatment is mandatory in the protocol.The CT-scan is planned to be done at the end of each of pair cycle, every 8-week but if it not done at the planned date, done at the next visit or at the end of the next cycle at the latest. Several visits could be performed by phone.Asymptomatic positive patients to Covid-19 are eligible to continue the study based on investigator's decision;Covid 19 symptomatic patients excluded of the study; Protocol amended is Protocol version v4.0 of 17-April-2020

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported