CLINICAL STUDY REPORT

Protocol number	:	C201
Title	:	Open, Non Controlled, Parallel Cohorts, Multicenter, Phase 2a study for the evaluation of the antitumor activity of GM102/Murlentamab single agent and in combination with chemotherapy in patients with locally advanced or metastatic colorectal cancer
Investigational product		Murlentamab (GM102)
Indication		Metastatic or locally advanced colorectal cancer
Development phase		Phase IIa
Study Coordinator		Prof. Eric Van Cutsem, MD Gastro-Enterology Unit UZ Leuven -Campus Gasthuisberg Herestraat 49, 3000 Leuven, Belgium
Sponsor		GamaMabs Pharma
Version/Date of report		18-OCT-2021, version 1.0

This study was carried out in compliance with Good Clinical Practice and ICH guidelines (International Conference of Harmonisation)

2. SYNOPSIS

Study title	Open, Non-Controlled, Parallel Cohorts, Multicenter, Phase 2a study for the evaluation of the antitumor activity of GM102/Murlentamab single agent and in combination with chemotherapy in patients with locally advanced or metastatic colorectal cancer
Investigational product	Murlentamab (GM102)
Indication studied	Locally advanced or metastatic colorectal cancer
Sponsor	GamaMabs Pharma
Study code	C201
Study Coordinator	Prof. Eric Van Cutsem, MD Gastro-Enterology Unit UZ Leuven – Campus Gasthuisberg Herestraat 49, 3000, Leuven, Belgium
Number of study sites	5 sites located in 2 European countries (Belgium, Czech Republic)
Study period	First Patient First Visit: 11-Jul-2018 Last Patient Last Visit: 10-Feb-2021
Phase of development	Phase IIa

Objectives

Primary objective

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

Secondary objectives

- To further evaluate the anti-tumor activity of murlentamab single agent and in combination with trifluridine/tipiracil with other efficacy parameters.
- To document the pharmacodynamic (PD) immunological effect of murlentamab on the tumor and its microenvironment (TME).
- To assess and document AMHRII expression on archived tumor samples, at study entry (baseline biopsy) and under murlentamab treatment (biopsy performed under treatment, optimally at end of C2).
- To confirm murlentamab single agent safety profile in the population of patients with advanced and metastatic colorectal cancer and to characterize murlentamab safety profile in combination with trifluridine/tipiracil.
- To characterize the systemic exposure of male and female patients

with CRC to murlentamab single agent and in combination with trifluridine/tipiracil.

- To assess the potential immunogenicity of murlentamab in this patient population.

Exploratory objectives:

- To document potential pharmacodynamic (PD) effect of murlentamab in immune blood cells.
- To assess an IHC assay under development for AMHRII detection.
- To investigate potential relationship between AMHRII levels and clinical outcome.
- To identify potential other biomarkers predictive of tumor response to murlentamab (Biobank).

Endpoints

Primary endpoints

- 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.

- Progression free survival (PFS) at 6 months.

Secondary endpoints

- ORR was also assessed according to immune RECIST (iRECIST) criteria from the end of cycle 2.

- Clinical benefit rate (CBR) at each tumor evaluation (number and % of non-progressors, *i.e.* CR+PR+SD) using RECIST and iRECIST criteria.

- Tumor Growth Rate (TGR) pre and under treatment (at the first tumor evaluation under treatment).

Progression free survival (PFS).

- Overall Survival (OS).

- PD evaluation: Tumor Immune Micro Environment changes: Quantity/density and quality of immune cells, including macrophages (M1 and M2 and phenotype changes), total and subpopulations of T cells.

- Incidence of SAE and Treatment Emergent Adverse Event (TEAE) experienced throughout the study period using NCI-CTCAE version 4.03.

- Exposure to murlentamab as a single agent and in combination with trifluridine/tipiracil was assessed through PK parameters analysis by nonlinear mixed effect modelling.

- Exposure of patients to trifluridine in Cohort II was assessed through description of trifluridine plasma concentrations in PK samples in the first 18 patients enrolled in Cohort II.

- Evidence of anti-murlentamab antibodies (ADA) at screening, at the beginning of every even cycle (pre-dose), and at the end of treatment visit.

Exploratory endpoints

- Evolution of quantification and qualification of circulating (peripheral blood) immune cells, including T cells and monocytes characteristics and activation under murlentamab.

- Assessment of AMHRII expression with IHC assay on patient archived

	tumor samples, on baseline and under treatment biopsies, and potential relationship with patient clinical outcome. - Other circulating or tumor-based biomarkers predictive of sensitivity to murlentamab may be assessed (Biobank).
Methodology	This was a multinational, multicentre, open, non-controlled study with a parallel group design. Patients suffering from confirmed locally advanced or metastatic colorectal cancer were considered for inclusion. Patients were including according to their profile and I nvestigator's judgement to one of the two following treatment groups with a 1:1 ratio: Cohort I (murlentamab alone) or Cohort II (murlentamab in combination with Trifluridine/Tipiracil). Recruitment of patients per site was not limited and was competitive across countries and sites. Study data were collected through an electronic case report form (eCRF) after the Investigator had obtained written informed consent form from the patient.
Number of patients	In the initial phase of the study 30 patients were planned to be enrolled (15 evaluable patients per group). In January 2020, the expansion phase of the study allowed enrolment of 20 to 25 additional patients in Cohort II. In total, 73 patients were included and 65 treated (18 in Cohort I and 47 in Cohort II)
Inclusion and exclusion criteria	The study population consisted of adult male and female patients suffering from confirmed locally advanced or metastatic colorectal cancer (CRC). Female and male patients were eligible for inclusion into the study if all of the following criteria were met: 1. Histologically-confirmed metastatic or locally advanced colorectal adenocarcinoma, 2. Having failed the previous line of treatment for locally advanced or metastatic disease and having received at least two systemic chemotherapy regimens for metastatic colorectal cancer; adjuvant regimen can be considered as one chemotherapy regimen for metastatic disease if the participant had disease recurrence within 6 months of completion, 3. At least one of the tumor sites amenable to core needle biopsy (may not be the site of disease for measuring antitumor response). Patient must agree to this pre-treatment biopsy and on a second biopsy under treatment (if the second biopsy cannot be performed, patients will continue on the study and will be considered evaluable for efficacy), 4. Available archived CRC tumor tissue sample, 5. At least one measurable lesion (≥ 1.0 cm longest diameter or ≥ 1.5 cm in short axis for malignant lymph nodes) based on RECIST 1.1 on the screening CT-scan, 6. Written Informed Consent forms signed, 7. Willing and able to comply with the trial requirements,

8. Covered by healthcare insurance in accordance with local requirements,

Specific to each cohort:

9. Cohort I (single agent murlentamab): refractory patients, having exhausted all therapeutic options.
   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.

The following exclusion criteria had also not to be fulfilled:

1. Age < 18 years old,
2. ECOG performance status ≥ 2,
3. Life expectancy < 12 weeks,
4. Major surgery or radiotherapy within 21 days prior to Cycle 1 Day 1 or anticipation of needing such procedure while receiving study treatment,
5. Known or symptomatic brain metastasis (other than totally resected or previously irradiated and non-progressive/relapsing) or lepto-meningeal carcinomatosis,
6. Concurrent treatment with any other anticancer therapy (or investigational agent) or received any anticancer therapy (or investigational agent) within 4 weeks prior to first treatment,
7. Known severe anaphylactic or other hypersensitivity reactions to IMP and/or its excipients,
8. Unresolved toxicity ≥ grade 2 according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 attributed to any prior therapies (excluding anemia, alopecia, skin pigmentation, and platinum induced neurotoxicity,
9. Serious concomitant illness, *e.g.* active infection requiring systemic antibiotic, antifungal or antiviral drug, or physical examination or laboratory abnormalities, that, in the opinion of the Investigator, would compromise protocol objectives,
10. Poor bone marrow reserve as defined by WBC < 3.0 x 10^9/L, neutrophils < 1.5 x 10^9/L or haemoglobin < 9.0 g/dL or platelet count < 100 x 10^9/L,
11. Poor organ function as defined by any one of the following:
    - Serum creatinine > 1.5 x ULN
    - Total bilirubin > 1.5 x ULN or > 2.5 x ULN if due to Gilbert's syndrome
    - AST, ALT > 2.5 x ULN in the absence of liver metastasis or > 5 x ULN in case of documented liver metastasis,
12. Severe New York Heart Association (NYHA) III and IV heart failure,
13. Pregnancy or breastfeeding,
14. Patient with reproductive potential who does not agree to use an accepted highly effective method of contraception – per

nvestigator's judgment - during the study period and for at least 6 months following completion of study treatment,
15. Patient deprived of liberty by a judicial or administrative decision, patient admitted to a social institution or who is under a measure of legal protection, patient hospitalized without consent or who is in an emergency situation,
16. Known allergy to rodents,
17. Patients positive to Covid-19.

Study treatment

Murlentamab (GM102) is a humanized glyco-engineered IgG1 antibody targeting AMHRII. 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, and following a loading dose of 10 mg/kg weekly during 28-day cycle 1 for patients of expansion cohort.

Trifluridine/tipiracil (Lonsurf) is comprised of an antineoplastic thymidine-based nucleoside analogue, trifluridine, and the thymidine phosphorylase (TPase) inhibitor, tipiracil hydrochloride, at a molar ratio 1:0.5, to be administered orally at the recommended dose of 35mg/m²/dose twice daily on Days 1 to 5 and Days 8 to 12 of each 28-day cycle.

Reference treatment

Not applicable

Duration of treatment

Patients received the study treatment (Investigational Medicinal Product, IMP) until progression or confirmed disease progression, unacceptable toxicity, death, withdrawal of consent (for any reason), non-compliance to the protocol or if the Investigator considered that it was no longer in the patient's best interest to continue the IMPs treatment

Study procedures

- Blood samplings for safety parameters assessments and central laboratory analysis were to be performed at baseline (within 2 weeks before treatment initiation) and at several timepoints during treatment,
- Tumoral biopsy were to be performed at screening (within 6 weeks before treatment initiation) and during the treatment period (ideally at end of cycle 2),
- CT-scans were to be performed at screening (within 6 weeks before treatment initiation) and at the end of every even cycle.

Sample size

In Cohort I the sample size was 15 calculated on ORR as follows. If one patient out of 15 was responder (*i.e.* corresponding to an Overall Response Rate (ORR) of 1/15 = 6.7%) then the probability that the true ORR was greater than 5% is approximately 64%. If two responders were observed (*i.e.* corresponding to an ORR of 2/15 = 13.3%) then the probability that the true ORR is greater than 10% was approximately 82%.

Therefore, 15 evaluable patients seemed to be sufficient to detect a signal of activity (*i.e.* at least one evaluable patient achieves a partial or complete response) in Cohort I.

In Cohort II the same rationale was used for the first 15 patients. Then, with the addition of the expansion Cohort, the sample size was increased from 15 to between 35 to 45 evaluable patients and calculated as follows.

For the primary endpoint ORR, if two patients out of 35 were responders (*i.e.* corresponding to an ORR of 2/35 = 5.7%) then the probability that the true ORR was greater than 2% is approximately 82%. This value of 2% is greater than the 1.6% responders for trifluridine/tipiracil single agent.

For the primary endpoint, Progression Free Survival (PFS) at 6 months, if eight patients out of 35 were free of progression (*i.e*. corresponding to a PFS at 6 months of 8/35 = 22.9%) then the probability that the true PFS at 6 months was greater than 15% is approximately 85%. This value of 15% is higher than the 12-13% patients free of progression for trifluridine/tipiracil single agent.

Therefore, 35 evaluable patients seemed sufficient to detect a signal of activity in Cohort II.

Statistical methods

Four data sets were defined for efficacy and tolerability analyses:

- 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);
- The 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;
- The 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;
- The 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.
- A 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.

Efficacy analyses have been summarized by cohort.

For the primary efficacy criterion, two primary endpoints of the study were defined and analysed for each cohort as follows:

- the Overall Tumor Response Rate (ORR) defined as the proportion of patients who achieved partial or complete response using RECIST criteria (Response Evaluation Criteria in Solid Tumors version 1.1, see **Appendix** Erreur ! Source du renvoi introuvable., protocol section **Erreur ! Source du renvoi introuvable.**Appendix 2) from the end of cycle 2 (*i.e.* 8 weeks) and subsequently confirmed at least 4 weeks later. Response was assessed in each site by the investigators and also externally reviewed by an Independent Radiological Committee (IRC). Both review data (per Investigator and per IRC) were reported. Discrepancies were investigated retrospectively. For each cohort, the ORR was estimated along with its 95% two-sided exact binomial (Clopper-Pearson) Confidence Intervals (CIs).
- The PFS at 6 months defined as the proportion of patients who achieved a documented progression or death due to any cause. Patients without documented progression at 6 months were considered as responders. Proportions of patients at each time point who were non-progressors (radiologically - using RECIST and iRECIST criteria - and clinically) from the first administration of murlentamab (Cohort I) or murlentamab + trifluridine/tipiracil (Cohort II) were estimated along with their 95% two-sided confidence intervals. The analysis of PFS used investigator-assessed progression data.

To note that for Cohort II: the PFS at 6 months was estimated along with its 95% two-sided exact binomial (Clopper-Pearson) CIs.

Both cohorts were exploratory only: *i.e.* there is no planned testing procedure and therefore no a priori control of type I and II errors.
Sensitivity analysis was also done, based on the IRC-assessed response data. Possible discrepancies between both analyses were investigated.

The same analyses were performed in the ITT and PP sets and in the subgroup of patients with at least 20% of tumor cells expressing AMHRII at the membranous level.

Analyses of the secondary efficacy endpoints were performed in the Evaluable Set (EEP) and sensitivity analyses were performed in the ITT and PP sets.

Immune Objective Response Rate (iORR):

iORR based on iRECIST criteria was estimated along with its 95% two-sided confidence intervals.

Clinical Benefit Rate (CBR):

The proportion of patients who are non-progressors (radiologically and clinically, including responders and stabilized patients, using RECIST 1.1 and iRECIST criteria) at each tumor evaluation from the first administration of murlentamab (Cohort I) or murlentamab + trifluridine/tipiracil (Cohort II) was estimated along with their 95% two-sided confidence intervals.

Tumor Growth Rate (TGR):

TGR curves (pretreatment and after completion of 2 cycles, at the first on-treatment CT scan) was calculated and displayed for each patient

Progression-Free Survival (PFS):

PFS was defined as the time elapsed from the date of first infusion to the date of documented progression or death due to any cause, whichever occurs first. Patients without documented progression were censored at the date of last response assessment that is stable disease or better. The Kaplan Meier (K-M) survival curve and K-M median (if estimable), along with its 2-sided 95% confidence interval (CI) was provided for each cohort. Proportions of patients at each tumor evaluation who were non-progressors (radiologically - using RECIST and iRECIST criteria - and clinically,) from the first administration of GM102 (Cohort I) or GM102 + trifluridine/tipiracil (Cohort II) were estimated along with their 95% two-sided confidence intervals. The analysis of PFS primarily used investigator-assessed progression data. Sensitivity analyses also used IRC-assessed response data.

Overall Survival (OS):

The analysis of OS was based on the ITT set. OS was defined as the time elapsed from the date of first infusion to the date of death. Patients without documentation of death at the time of analysis were censored at the date last known to be alive. The Kaplan Meier (K-M) survival curve and K-M median (if estimable), along with its 2-sided 95% CI were provided for each cohort. The overall survival rates at each tumor evaluation were estimated from the K-M curves along with their 95% CI.

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Summary / Conclusions

Population:

From Jul-2018 to Mar-2020, 73 patients were screened in the 5 sites who participated in the study and 65 (89.0%) patients were enrolled. Overall, 81.8% of the enrolled patients completed 2 cycles (*i.e.* time point for primary endpoint criteria analysis). Eventually, all patients discontinued the treatment during the study. The main reason for treatment discontinuation was progression (radiological and/ or clinical): 95.2% (n=20) in the Cohort I, 94.4% (n=17) in Initial Cohort II and 100% (n=26) in Cohort II expansion. In addition, two patients discontinued the treatment due to death: one 34 year old male patient included in the Cohort I (general health deterioration resulting in death) and one 59 years old woman included in the Cohort II (disease progression resulting in death), respectively. Deaths were related to disease progression and not to murlentamab.

Median study duration was 3.09 months (Min ; Max: 1.9 ; 6.2) in Cohort I, 3.56 months (Min ; Max: 1.3 ; 15.9) in Initial Cohort II, and 5.17 months in Cohort II expansion (Min ; Max: 1.9 ; 13.8) respectively. The maximum number of cycles completed during the study was five in Cohort I (two patients, 9.5%), 16 in Initial Cohort II (one patient, 5.6%) and 12 in Cohort II expansion (one patient, 3.8%), respectively.

At the end of study (*i.e*. at the last patient last study visit in each Cohort), 12 patients (57.1%) of the Cohort I, 11 patients (61.1%) of the Initial Cohort II and 15 patients (57.7%) of the Cohort II expansion were still alive. A follow-up was performed for patients still alive before database freeze. Overall, only one patient (5.6%) included in the Initial Cohort II and six patients (23.1%) included in the Cohort II expansion were still alive.

AMHRII expression determined by IHC on baseline biopsy was available for 16 patients (76.2%) in Cohort I, 18 patients (100%) in Initial 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.

Baseline characteristics:

In the safety set of patients 58 % were male patients. Among the female patients, 25 (92.6%) were considered as “Post-menopausal” or “Sterile of childbearing age”. The median age was similar between cohorts: approximately 63 in Cohort I, 59 in Initial Cohort II and Cohort II expansion, respectively. Median weight at baseline and height were also similar between cohorts. Accordingly, BMI and BSA were similar as well.

All patients presented Grade 0 or 1 ECOG PS. 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. 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. 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. 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. 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). Resection was mainly considered as "R0" for most of the patients (n=26, 83.9%) ranging from 62.5% to 100%. Only few patients presenting mainly a rectum cancer benefited from radiotherapy. All patients presented metastasis at screening. 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. In addition, among them 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. 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.

In the end, six patients (28%) in Cohort I, nine patients (50%) in Initial Cohort II and three patients (11%) in Cohort II expansion progressed under primary 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) as compared to Initial Cohort II and Cohort II expansion that were similar (2.00 vs 2.50, respectively). The number of metastatic lines received ranged from one to seven in the Cohort I, one to four in the Initial Cohort II and one to six in 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, respectively. This difference in the number of previous lines of therapy reflects the difference in the inclusion criteria of Cohort I including patients having exhausted all therapeutic approaches, and of Cohort II including patients susceptible to be treated by Trifluridine/tipiracil.

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.

In addition, reflecting the superior seriousness of the disease, patients included in Cohort I were also frequently receiving Trifluridine/tipiracil (n=19, 90.5%) and regorafenib (47.6%, 22.2%, 19.2% in Cohort I, initial II and II expansion, respectively) when few patients included in Initial Cohort II and II expansion received these drugs. All the patients in the safety set had at least one other relevant medical history mainly in the vascular disorder System Organ Class (SOC) and the Gastrointestinal disorders SOC. The majority of patients had received prior medications not related to CRC treatment in the Safety Set. Regarding concomitant medications not related to CRC treatment, all patients were receiving at least one treatment.

Efficacy results:

Compliance,

Murlentamab compliance defined as a patient having received between 90-110% of the planned dose was calculated for all patients. Treatment compliance was good in all cohorts Cohort I and Initial Cohort II (100%, and 94.4%, and 84.6% respectively). The lowest compliance value was observed in Cohort II expansion in relation to all patients from site 04 who did not receive the loading dose (see Section 9.8.3, for details). In addition, median treatment adherence was of 100% in all cohorts. Trifluridine/tipiracil compliance in Cohort II overall was good: 94.4% in Initial Cohort II and 84.0% in Cohort II expansion.

Primary endpoint,

- 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. On the contrary, 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. Results obtained in the mITT (10/44) and PP (7/28) set were consistent with this result. In addition, sensitivity analysis performed according to IRC assessment confirmed these results.

Secondary endpoints

- Best response: Overall, only one patient in Cohort II expansion achieved a partial response as previously described. 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 Initial Cohort II and 15 patients (71.4%) in Cohort II expansion, respectively.
- Tumor Growth Rate: 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. Data obtained in the mITT set were consistent

with these results.

- Progression Free Survival: After two months, only one patient (7.7%), six patients (46.2%) and 11 patients (52.4%) were still considered as non-progressors in the Cohort I, initial Cohort II and II expansion, respectively. After 10 months, one patient (7.7%) and two patients (9.5%) were still at risk in initial 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 (p-value for Logrank test is 0.0186). On the contrary, the loading dose received in Cohort II overall did not seem to have an impact on PFS.
- Overall Survival: By the time of the analysis, after 36 months follow-up, 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).

Safety results:

All adverse events analysis were performed in the Safety Set (SS).

Overall, on the Safety Set, almost all patients reported at least an AE or a TEAE. During the study, 923 AEs have been recorded for 64 patients (98.5%): 21 patients in the Cohort I (100.0%), 18 patients in Cohort II (100.0%) and 25 patients in the Cohort II expansion (96.0%) experienced at least one AE. Among those 923 AEs, 875 (94.8%) were considered as TEAEs. Eighty-one (81) TEAEs related to murlentamab were reported in 29 patients out of the 65 patients treated in the C201 study: decreased appetite reported in 10 patients, and fatigue/asthenia reported in 8 patients. Nausea was reported in 6 patients, vomiting in 5 patients, diarrhea in 4 patients, and dysgeusia in 4 patients. Those symptoms are not unexpected in the context of patients suffering from serious and advanced digestive cancer. Among these events, 3 events of grade ≥ 3 observed in 3 patients. These 3 events are one grade 3 fatigue and two grade 3 neutropenia (which was also attributed to trifluridine/tiripacil).

Few of the TEAEs met the definition of serious events. Indeed, only 6.0%, 5.3% and 0.7% of these TEAE reported in Cohort I, Initial Cohort II and Cohort II expansion, respectively, were considered as serious. It corresponded to eight events in six patients (28%) of Cohort I, 13 events in five patients (27%) of Initial Cohort II and four events in four patients (15%) of Cohort II expansion. In addition, and as a reflect of the already recognized good tolerability of the product, especially from the C101 study results in gynecological tumors, none of these Serious TEAEs were related to murlentamab. Moreover, the majority of the TEAE reported in

the Initial Cohort II (n=142, 58.2%) and Cohort II expansion (n=293, 55.0%) were related to trifluridine/tiripacil (four neutropenia and one febrile neutropenia).

Conclusion

Altogether, the C201 study led to mixed results in terms of murlentamab antitumor activity. On the one hand, this study did not meet the first primary endpoint regarding ORR neither in Cohort I nor in the Cohort II overall. On the other hand, the second primary endpoint regarding PFS at 6 months was achieved (9 patients out of 34) in the Cohort II overall. In addition, the changes observed in the primary endpoints PFS at 6 months and the secondary endpoint such as best response, PFS and OS, appeared to be more pronounced (and in some cases statistically significant) in patients with high AMHRII expression (≥20% of tumor cells with membranous expression), which is consistent with the mechanism of action murlentamab (targeting specifically this receptor and subsequently activating immune cells). These results qualitatively validate the hypothesis according to AMHRII is expressed on CRC tumor cells and can be targeted to elicit a therapeutic activity via an antibody of high affinity like murlentamab. Moreover, we confirmed here the good tolerability of murlentamab alone or in combination.
However, taking into account both the lack of effect on ORR and the effect size observed on PFS at 6 months, these results were considered as insufficient to pursue the clinical development of murlentamab as a naked antibody in colorectal cancer.