Phase 1/2 dose escalation and cohort expansion study evaluating MCLA-158 (Petosemtamab) as single agent or in combination in advanced solid tumors

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This study has been transitioned to CTIS with ID 2024-513627-16-01 check the CTIS register for the current data. Dose escalationPrimary• To determine the RP2D of single-agent petosemtamab in mCRC patients who have progressed on chemotherapy, with or…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON56321

Source
ToetsingOnline

Brief title
Clinical study evaluating MCLA-158 in metastatic cancer

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
advanced solid tumors

Research involving
Human

Sponsors and support

Primary sponsor: Merus N.V.
Source(s) of monetary or material Support: Merus N.V.

Intervention

Keyword: advanced solid tumors

Outcome measures

Primary outcome

Dose escalation:

• To determine the preliminary RP2D of single-agent petosemtamab in mCRC patients who have progressed on chemotherapy, with or without an anti-vascular endothelial growth factor (VEGF) therapy, and with an anti-EGFR therapy (if RASwt)

Dose expansion (single agent- non-randomized expansion cohorts):

• To determine the overall response rate (ORR) per RECIST 1.1 (per investigator review)

Dose expansion (single agent, randomized expansion in HNSCC 2/3L):

• To descriptively characterize all relevant clinical safety and efficacy data within the study

• To characterize the exposure-safety relationship of petosemtamab administered at 1100 mg and 1500 mg Q2W in terms of TEAEs

Dose expansion (combination):

• To determine the overall response rate (ORR) per RECIST 1.1 (per

investigator review)

• To characterize safety and tolerability for combinations.

Dose expansion (combination, 2L mCRC cohort)

• To characterize safety and tolerability for petosemtamab in

combination with FOLFIRI/FOLFOX

Secondary outcome

Dose escalation:

safety and tolerability

PK

immunogenicity

biomarkers in tumor samples relevant to EGFR and LGR5 and early tumor response

profile

preliminary antitumor activity

Dose exp. (single agent/combination):

antitumor activity in terms of PFS, DOR RECIST 1.1 (per investigator)

and in exp. cohorts with antitumor activity observed (per central review)

OS

safety/tolerability of single-agent peto. and confirm the RP2D

PK of peto. (single agent) and of peto. in combo with pembro.FOLFOX/FOLFIRI

immunogenicity of peto.

biomarkers relevant to EGFR and LGR5 and tumor response of peto.

Dose exp. (single agent, randomized exp. in HNSCC 2/3L):

exposure-efficacy relationship of peto. at 1100 mg and 1500 mg Q2W:

sum of lesions and in terms of Grade 3-4 TEAEs, IRRs and non-IRR TEAEs

other safety

PK

immunogenicity

antitumor activity: ORR, DOR, PFS RECIST 1.1 (per

investigator/centralreview)

biomarkers in samples relevant to EGFR and LGR5 as well as the early

tumor response profile

Study description

Background summary

Colorectal cancer (CRC) is the third most-diagnosed cancer in Europe and the United States, and 30% of patients with CRC present with metastatic disease (Schmoll et al, 2012; Torre et al, 2015). Epidermal growth factor receptor (EGFR) is frequently mutated or overexpressed in CRC and many other cancers including the lung, colon, head and neck, and pancreas among others. Antibodies targeting the extracellular domain of EGFR and small molecule inhibitors targeting the intracellular kinase domain of EGFR are used extensively in the standard of care management of these cancers.
Leucine-rich repeat-containing G-protein coupled receptor 5 (LGR5) is a G-protein-coupled, seven-transmembrane-domain receptor for R-spondins which are potent WNT signal enhancers and stem cell growth factors (de Lau et al, 2011). It is present in intestinal stem cells found in the base of intestinal crypts, and other normal differentiated cell types including brain, endometrium, muscle, ovary and pancreas. LGR5 is highly regulated and maintains a small number of native stem cells in their undifferentiated state in the base of the colonic crypt. It is also expressed in primary and metastatic colon cancer in animal models (de Sousa e Melo et al, 2017; Shimokawa et al, 2017) and LGR5-positive cells have been shown to play a role of in establishing and maintaining liver metastasis. Cancer stem cells (CSCs) of various origins including colorectal cancer (CRC) stem cells are LGR5-positive. WNT has also

been shown to be an oncogenic driver in many cancers, and is the most commonly altered pathway in CRC. Dysregulation of the WNT/β-catenin axis results in uncontrolled proliferation and dissemination of CSCs that form the primary tumor and ultimately metastatic lesions. LGR5 signal enhancement is proposed to be important in stem cell renewal, maintaining cells in the stem cell program, and the upregulation of LGR5 expression observed in adenocarcinomas (Martin et al, 2017) is consistent with the link between WNT signal strength, stem cell signature, and colon CSC behavior.

Rationale for developing MCLA-158 in EGFR-driven tumors

MCLA-158 is a common light chain human full-length IgG1 bispecific antibody with enhanced ADCC activity, targeting the EGFR and the LGR5, two receptors which are critical for the growth and survival of CSCs. The convergence of the WNT and EGFR signaling pathways provides both oncogenic and mitogenic drivers in CRC stem cells. CRC stem cells play a central role not only in tumor initiation and growth, but also in tumor relapse and resistance to anticancer therapies.

Via its bispecific mode of action, it is hypothesized that MCLA-158 induces antitumor activity by simultaneously binding and blocking oncogenic drivers and proliferative signaling in CRC stem cells. MCLA-158*s enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) properties are expected to augment these antitumor effects via the recruitment of immune effector cells that directly kill tumors. MCLA-158 has demonstrated strong inhibitory growth activity in patient-derived tumor organoids and was significantly more active in organoids derived from CRC tumors than from normal tissue. Importantly normal tissue organoids are dependent on R-spondin for growth but the activity of MCLA-158 in normal organoids was no different to that of the EGFR-targeting antibody cetuximab. The bispecific format of MCLA-158 confers greater potency than combining each targeting arm against LGR5 and EGFR as separate monoclonal antibodies. In vivo experiments with patient-derived and organoid-derived xenografts have demonstrated activity in RAS wildtype (RASwt) and RAS mutant (RASmut) CRC models. Beyond CRC, activity has been observed in patient-derived xenograft (PDX) models that co-express elevated LGR5 and EGFR mRNA levels according to RNA sequencing data. MCLA-158 demonstrated significant antitumor activity in the majority of PDX models of head and neck squamous cancer, gastric adenocarcinoma, and esophageal squamous cell carcinoma, in both the KRASwt and KRASmut settings. While MCLA-158 inhibits EGFR signaling, the LGR5 arm acts as a simple docker of the antibody targeting it to CRC cells, and does not appear to block R-spondin binding to LGR5 or modulate the WNT signaling pathway, consistent with its lack of activity in normal tissue organoids.

Planned early MCLA-158 development

The clinical strategy for the development of MCLA-158 involves a phase 1/2 study with an initial dose-finding part for single-agent MCLA-158 in mCRC patients progressing on oxaliplatin- and irinotecan-based chemotherapies ± antiangiogenic therapy to determine the recommended phase 2 dose (RP2D). In an expansion part, activity, safety, and tolerability of MCLA-158 at the

single-agent R2PD will be evaluated in cohorts of selected solid tumor indications with dependency on EGFR signaling. Eligible indications may include locally advanced unresectable or metastatic head and neck squamous cell carcinoma (HNSCC), anogenital squamous cell carcinoma (SCC), non-small cell lung cancer (NSCLC; SCC and non-SCC), gastric/gastroesophageal junction adenocarcinoma with EGFR amplification or high EGFR expression, endometrial adenocarcinoma, pancreatic adenocarcinoma, and CRC KRASwt.

Study objective

This study has been transitioned to CTIS with ID 2024-513627-16-01 check the CTIS register for the current data.

Dose escalation
Primary
• To determine the RP2D of single-agent petosemtamab in mCRC patients who have progressed on chemotherapy, with or without an anti-VEGF therapy, and with an anti-EGFR therapy (if RASwt)

Secondary
• To characterize the safety and tolerability of petosemtamab
• To evaluate preliminary antitumor activity
• To characterize the PK of petosemtamab
• To characterize the immunogenicity of petosemtamab
• To correlate biomarkers in tumor samples relevant to EGFR and LGR5 as well as the early tumor response profile of petosemtamab

Exploratory
• To explore additional biomarkers in tumor and blood samples (circulating free deoxyribonucleic acid [DNA], cancer cells and proteins) predictive of response or resistance to therapy.
• To evaluate the mutational status and other genetic alterations or gene expression status of a panel of genes on (archival) tumor biopsies as potential selection biomarkers for patient stratification.
• To evaluate potential pharmacodynamics (PD) biomarkers in response to therapy
• To evaluate further biomarkers to investigate the drug (ie, mode-of-action-related effect and/or safety) and/or the pathomechanism of the disease

Dose Expansion Single agent
Primary
• To determine the ORR per RECIST 1.1 (per investigator review)
Secondary
• To evaluate antitumor activity in terms of PFS and DOR per RECIST 1.1 (per investigator review)
• To evaluate antitumor activity in terms of ORR and DOR per RECIST 1.1 in expansion cohorts with preliminary antitumor activity observed (per central

review)
• To evaluate OS
• To characterize safety and tolerability of single-agent petosemtamab and confirm the RP2D
• To characterize the PK of petosemtamab
• To characterize the immunogenicity of petosemtamab
• To correlate biomarkers in tumor samples relevant to EGFR and LGR5 as well as the early tumor response profile of petosemtamab

Exploratory
• To explore additional biomarkers in tumor and blood samples (circulating free nucleic acids, cancer cells, and proteins) predictive of response or resistance to therapy
• To evaluate the mutational status and other genetic alterations or gene expression status of a panel of genes on (archival) tumor biopsies as potential selection biomarkers for patient stratification
• To evaluate potential PD biomarkers in response to therapy
• To evaluate further biomarkers to investigate the drug (ie, mode-of-action-related effect and/or safety) and/or the pathomechanism of the disease

Dose Expansion Combination
Primary
• To determine the ORR per RECIST 1.1 (per investigator review)
• To characterize safety and tolerability for combinations
Secondary
• To evaluate antitumor activity in PFS and DOR per RECIST 1.1 (per investigator review)
• To evaluate antitumor activity in terms of ORR and DOR per RECIST 1.1 (per central review)
• To evaluate OS
• To characterize safety and tolerability of petosemtamab in combination with pembrolizumab as well as to further evaluate RP2D
• To characterize the PK of petosemtamab in combination with pembrolizumab
• To characterize the immunogenicity of petosemtamab
• To correlate biomarkers in tumor samples relevant to EGFR and LGR5 as well as the early tumor response profile of petosemtamab

Exploratory
• To explore additional biomarkers in tumor and blood samples (circulating free nucleic acids, cancer cells, and proteins) predictive of response or resistance to therapy
• To evaluate the mutational status and other genetic alterations or gene expression status of a panel of genes on (archival) tumor biopsies as potential selection biomarkers for patient stratification
• To evaluate potential PD biomarkers in response to therapy
• To evaluate further biomarkers to investigate the drug (ie,

mode-of-action-related effect and/or safety) and/or the pathomechanism of the disease

Dose expansion (combination, 2L mCRC cohort)
• To characterize safety and tolerability for petosemtamab in combination with FOLFIRI/FOLFOX

Study design

This is a FIH phase 1/2 open-label multicenter study combining an initial dose escalation part with a dose expansion part (in both single-agent and combination cohorts). The initial dose escalation part was completed, and the preliminary RP2D was established at 1500 mg Q2W (see Section 3.1.1).
At the time of implementation of this amendment, patients who are already on treatment or in follow up will continue to follow assessments in protocol amendment v 6.0 (dated 04 MAY 2023), while new patients treated under this amendment will be governed by this protocol amendment.
Single-agent or combination cohorts of selected solid tumor indications for which there is evidence of EGFR dependency and potential sensitivity to EGFR inhibition will be evaluated in a dose expansion part of the study. The eligible solid tumor indications are specified in the petosemtamab development section above.

Tumor samples will be analyzed in central laboratories (unless otherwise stated), using a Sponsor-approved test in accordance with local clinical testing regulations, for potential biomarkers retrospectively and by immunohistochemistry (IHC) if available at the investigational site. Patients must sign a screening informed consent form (ICF) before the sample is submitted for analysis

When the ICF is signed, a screening period of 28 days will start (see Section 3.3). All screening procedures should take place within 28 days prior to the patient's first dose, including the baseline tumor biopsy (see Section 12.2.1).
Petosemtamab will be administered IV as a flat dose over an infusion period of 2 to approximately 6 h, Q2W, with 4-week cycles (28 days). As of 22 January 2021, 1500 mg Q2W is the primary dose level under investigation in the dose expansion cohorts with demonstration of clinical activity.
Approximately 567 patients will be assigned to 1 of 7 possible dose expansion treatment arms: 4 arms using petosemtamab as a single agent and 3 arms using petosemtamab in combination with other agents as shown in the above diagram and explained further in Section 3.1.1.
Safety, PK, immunogenicity, and antitumor activity of single-agent petosemtamab will be characterized in all cohort patients, and retrospective biomarker analyses including EGFR and LGR5 status will be performed.
A Safety Monitoring Committee (SMC) composed of the principal investigators, the Sponsor*s medical expert(s), and safety and PK representatives, will review data according to the SMC charter at designated timepoints throughout the study

and advise on DLTs, addition of extra patients at a given dose, and dose escalation or de-escalation. The SMC or Sponsor may propose opening dose expansion cohorts and advise on safety decisions, including the modification of dosing increments, de-escalations, and dosing frequency (see Sections 3.1.6 and 9.14).
The Sponsor will monitor safety on an ongoing basis, and instruct sites on measures for monitoring IRRs.
Dose escalation safety evaluation
The planned dose escalation part of the study has been completed. Allometric scaling of a nonclinical PK model was used to predict petosemtamab exposure in humans. The petosemtamab starting dose was 5 mg (flat dose) IV, Q2W, with 4-week cycles. Up to 11 dose levels were investigated: 5, 20, 50, 90, 150, 225, 335, 500, 750, 1100 and 1500 mg (flat dose), Q2W. The administered dose, dose increments, and frequency of dosing for each patient and each cohort was subject to change based on patient safety, PK and PD data, and upon recommendation of the SMC.
An accelerated Simon design was implemented to evaluate safety during dose escalation.
To be evaluable for a DLT, patients had to receive the intended petosemtamab dose for the first 28-day cycle, or experience a DLT. Patients not evaluable for DLT were replaced (see Section 3.1.4.1).
Dose expansion and combination safety evaluation
For the dose expansion (both single-agent and combination) cohorts, safety evaluation will follow the guidelines

Intervention

INVESTIGATIONAL THERAPY AND REGIMEN MCLA-158: IV infusion every 2 weeks, with a starting dose of 5 mg (flat dose). The following dose levels were planned: 5, 20, 50, 90, 150, 225, 335, 500, 750, 1100 and 1500 mg (flat dose). Dose escalation was halted once the RP2D to investigate further in the expansion part was selected. The administered dose, dose increments, and frequency of dosing for each patient and each cohort is subject to change based on patient safety, PK and PD data, and upon recommendation of the SMC. As of 22 January 2021, 1500 mg Q2W is the dose level under investigation in the expansion part with demonstration of clinical activity. Infusions must be administered over a minimum of 4 hours during Cycle 1. Details of MCLA-158 administration over the minimum 4 hours are provided in separate Study Specific Dosing Instructions. Subsequent infusions after Cycle 1 can be reduced to 2 hours at the investigator*s discretion and in the absence of IRRs. A mandatory premedication regimen (dexamethasone, antihistamines, paracetamol) is administered for all infusions in Cycle 1, initiated within 24 hours prior to each infusion with optional premedication with dexamethasone for subsequent infusions in the absence of severe IRRs. A cycle is considered 4 weeks. For each patient, a 6-hour observation period will be implemented following infusion start for the initial MCLA-158 infusion, a 4-hour period for the second infusion, and a minimum of 2 hours for all subsequent administrations, corresponding to at

least the duration of the infusion. Treatment adaptation • MCLA-158 infusion will be interrupted immediately in the event of an infusion-related reaction (IRR) and symptomatic treatment will be administered. For mild to moderate events (grade 1-2) after marked clinical improvement, the infusion can be resumed at a 50% infusion rate. For grade 3 events, it is up to the investigator*s judgment whether to resume the infusion at the 50% rate or to stop MCLA-158. For grade 4 events, MCLA-158 must be stopped definitively. • Dose reductions, interruptions and symptomatic treatment will be implemented in the event of dermatologic toxicities, diarrhea/vomiting, hypomagnesemia, thrombocytopenia, and neutropenia (see protocol section 5.3.3). • MCLA-158 administration can be delayed to manage AEs for a maximum of 2 infusions (i.e., up to 6 weeks between two consecutive infusions). Treatment duration Study treatment will be administered until confirmed progressive disease (as per RECIST 1.1), unacceptable toxicity, withdrawal of consent, patient non-compliance, investigator decision (e.g., clinical deterioration), or MCLA-158 interruption >6 consecutive weeks. Patients will be followed up for safety for at least 30 days following the last MCLA-158 infusion and until recovery or stabilization of all related toxicities, and for disease progression and survival status for 12 months. In protocol version 5 a combination cohort with Pembrolizumab and MCLA-158 is added. Patients with HNSCC in first lmine will be treated in this cohort.

Study burden and risks

· Risk of infusion-related reactions (IRRs) and/or hypersensitivity
Antibodies like petosemtamab can cause a reaction when given by infusion. These are called IRRs. IRRs can include hypotension (low blood pressure), shortness of breath, skin redness, nausea, headache, fever, chills, tremor, excessive sweating, itching, tachycardia, and/or vomiting. These reactions might be mild, moderate, or serious. Out of the 79 patients treated, 72% experienced an IRR. Most of these IRRs were mild to moderate with 6 patients discontinuing treatment due to their IRR. IRRs typically occur during or after the first infusion of the therapeutic antibodies, and may improve or stop altogether on later infusions.
· Skin side effects
Study drugs like petosemtamab, which target an area on cells called the EGFR receptor, can cause skin related side effects. Out of the 79 patients treated, 35% experienced rash, 25% dermatitis acneiform, 19% redness, 14% itching, 10% dry skin and skin fissures, 8% bumps around your hair follicles (which may become sores), 6% skin toxicity and 5% excessive sweating. Most of these events were mild to moderate with 1 out of 79 patients experiencing severe dermatitis acneiform, bumps around hair follicles, skin toxicity and excessive sweating.
· Gastrointestinal side effects
Study drugs like petosemtamab, which target an area on cells called the EGFR receptor, can also cause side effects affecting the gastrointestinal system. Out of the 79 patients treated 18% experienced nausea, 9% diarrhea and inflammation of the mucous membranes of the mouth and 5% vomiting. All these

events were mild to moderate. 1 out of 79 patients experienced severe abdominal discomfort.
· Other side effects
Out of the 79 patients treated, 17% experienced a decrease in blood magnesium levels, 8% skin infections around the nail, 6% decrease in white blood cells, weakness and fatigue. 5% had patches of red bumps with pus and 5% experienced a syncope.

Other potential risks seen in drugs that target the EGFR receptor are shown below:
· Other EGFR-related risks
Other potential risks seen include conjunctivitis (*pink eye*), swelling of the eyelids, increased tear production (*watery eyes*), decrease of potassium levels in the blood, and respiratory symptoms such as scarring in the lungs or other related lung conditions. To date, some of these risks have been observed, and assessed as related, in patients treated at 1500mg Q2W. Events included dry eye (3 patients) and lacrimation increased, eye pruritus, scleral hyperemia, vision blurred and keratopathy in 1 patient each.
· LGR5-related risks
As described previously, petosemtamab also attaches to an area on cells called the LGR5 receptor, which is part of a system called the WNT pathway. There is not enough information available about side effects caused by antibodies targeting the LGR5 in humans so the likelihood of side effects is difficult to predict. As LGR5 is present on both tumoral and normal intestinal stem cells, as well as other cells that may be critical for normal tissue function, targeting LGR5 cells as a therapeutic anticancer strategy may also impact normal tissue functioning. Concerns of effects on intestinal stem cells (Gastrointestinal toxicity), bone turnover (risk of bone fracture) and hematopoiesis (myelosuppression) will be taken into consideration in clinical studies with petosemtamab.

Pregnancy and Reproductive Risks

The potential risks of MCLA-158 on human reproductive function and on the human fetus have not yet been studied. Women must not therefore become pregnant or breast-feed while participating in the study. As a result, if you (or your sexual partner) are of child-bearing potential, you must use an effective method of contraception throughout the clinical study and for 6 months after the last dose of MCLA-158. Effective methods of contraception include: true abstinence, or a sole partner who is vasectomized, or a combination of two of the following: intrauterine device/system, a condom with spermicidal foam/gel/film/cream/suppository, and an occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam, gel, film, cream or suppository. The use of hormonal methods of contraception are not considered effective enough for this clinical study.

If you do become pregnant during the clinical study, you must inform your investigating doctor and you will no longer be able to take part in this clinical study. If you or your partner becomes pregnant during the trial or within six (6) months of stopping treatment, your trial team will discuss all the options available to you. The outcome and progress of any pregnancy will be followed by your trial team, and you will be asked questions about the pregnancy and baby, if appropriate.

As MCLA-158 is a new drug being developed there may be other side effects that are not yet known.
5. Other side effects associated with medical procedures used during the clinical study
Blood draws, where samples of your blood are taken to run laboratory tests, are standard practice in your illness and are not specific to this clinical study. However, there may be more blood draws than usual which may make you more susceptible to side effects (pain, bruising, inflammation and swelling of the vein, bleeding or even an infection at the puncture site).
CT scans, magnetic resonance imaging (MRI) and bone scans are normally carried out to diagnose and assess your disease and those done in this clinical study are not expected to be different. However, there may be more of these procedures than you are used to.
A CT scan is a series of x-rays put together by a computer. CT scans will expose you to small amounts of radiation. Although repeated radiation may damage body tissues and slightly increase chances of having cancer, the risk from the imaging being done for this clinical study is not considered to be significant.
Magnetic resonance imaging (MRI) is a technique that uses a magnetic field and radio waves to create detailed images of the organs and tissues within your body.
CT scans and MRI scans involve dyes (called *contrast medium*) being injected into one of your veins to help the organs in your body and your cancer to show up on the scans. There is a risk that you may have an allergic reaction to the dye. This reaction may be mild (such as a skin rash or hives) or severe (such as breathing difficulties and shock). In rare instances, severe or fatal allergic reactions have been reported (0.001-0.0002% of cases).
Both CT and MRI scans mean lying still in a confined space for a period of time, so you should consider this, if you suffer from claustrophobia.
A bone scan is a nuclear medicine test which helps find cancer that has started in or has spread to the bones. This means that the procedure uses a very small amount of a radioactive substance, called a tracer. The tracer is injected into a vein. The tracers in the radioactive dye used in a bone scan produce very little radiation exposure. Even the risk of having an allergic reaction to the tracers is low. Bone scans will only be performed if your cancer has spread to your bones.
A multigated acquisition (MUGA) scan is a nuclear medicine imaging test that checks how well the heart is pumping during rest or exercise. A MUGA scan uses a radioactive material (radiopharmaceutical) that targets the heart, along with

a gamma camera and a computer, to create images of the blood flowing through the heart.
A MUGA scan is also called nuclear ventriculography, radionuclide angiography or cardiac blood pool scan.
The dose of x-rays or radioactive materials used in nuclear medicine imaging can be different for every test. The dose depends on the type of procedure and body part being examined. In general, the dose of radioactive material given is small and you are exposed to low levels of radiation during the test. The benefit

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Signed ICF before initiation of any study procedures

2. Age >=18 years at signing of ICF
3. Histologically or cytologically confirmed solid tumors with evidence of metastatic or locally advanced disease not amenable to standard therapy with curative intent:
• Expansion cohorts: patients with locally advanced unresectable or metastatic disease for the following indications:
SINGLE AGENT
o 2L/3L HNSCC PATIENTS: patients who have progressed on or after, or are intolerant to, anti-PD-(L)1 and platinum therapy as monotherapy or in combination with other agents and no previous exposure to EGFR inhibitors. Patients treated with platinum-containing therapy only in the adjuvant setting, or in the context of multimodal therapy for locally advanced disease, should have disease progression within 6 months of the last dose of platinum containing therapy. Patients should not have received more than 2 prior lines of treatment in recurrent or metastatic disease.
* Human papillomavirus (HPV) status determined by p16 IHC or molecular HPV test for all oropharyngeal tumors should be reported when available.
* The eligible HNSCC primary tumor locations are oropharynx, oral cavity, hypopharynx, and larynx.
o Cancers of the anogenital tract with squamous cell histology (ie, cervical, vaginal, vulvar, penile, anal)
o Skin SCC
o NSCLC non-SCC and NSCLC SCC
o GEA with histologically confirmed EGFR amplification (fluorescence in situ hybridization [FISH] score EGFR/ chromosome 7 (CEP7) ratio >=2.0, or tumor NGS EGFR copy >=8, or ctDNA >=4, or EGFR IHC H-score >=200)
o PA
o mCRC in 3L+: Patients should be free of mutations in RAS family genes (i.e. KRAS, NRAS, Harvey Rat Sarcoma virus [HRAS], or RAF family genes (i.e. BRAF, A-Rapidly Accelerated Fibrosarcoma [ARAF}, Rapidly Accelerated Fibrosarcoma-1 [RAF1]), determined by central ctDNA NGS prescreening]). Note: If the patient was treated with an EGFR inhibitor in 1L or 2L, then the patient should have shown CR/PR. In addition, the patient at study entry should have at least 6 months of interval since the last administration of EGFR inhibitor.
Other indications may be considered, such as malignant salivary gland tumors.
• Note 1: Patients with NSCLC must receive all recommended standard therapies driven by the histological subtype and tumor molecular profile.
• Note 2: Patients with other indications must have been previously treated with 1 or 2 lines of the standard approved therapy (when applicable) in the locally advanced/unresectable or metastatic setting.
COMBINATION
o 1L HNSCC: patients eligible to receive pembrolizumab as 1L monotherapy with tumors expressing PD-L1, CPS >=1, as determined by an FDA-approved test in the US, or by an approved equivalent test in other countries; patients should not have previous systemic therapy administered in the recurrent or metastatic setting, although previous systemic therapy as part of multimodal treatment for locally advance disease is allowed if ended >=6 months prior to signing the ICF.

The eligible HNSCC primary tumor locations are oropharynx, oral cavity, hypopharynx, and larynx. Previous treatments with anti-PD-(L)1 or anti-EGFR therapies are not allowed.
o 2L mCRC: Patients should have been previously diagnosed with histologically or cytologically confirmed unresectable or metastatic adenocarcinoma of the colon or rectum. Patients must be RAS/RAF WT as determined using NGS on tumor tissue (primary or metastatic) or other appropriate tumor tissue based assay, to be confirmed by the sponsor. Patients must be naive to prior anti-EGFR therapy. Radiographically confirmed disease progression must have occurred during or within 6 months of prior 1L chemotherapy.
o Cohort to be treated with petosemtamab and FOLFIRI: patients should have had only 1 prior chemotherapy regimen for the metastatic setting, consisting of 1L fluoropyrimidine-oxaliplatin-based chemotherapy ± bevacizumab. Note: FOLFOX-based adjuvant treatment would be considered front-line if PD occurred within 6 months of completion of adjuvant therapy.
o Cohort to be treated with petosemtamab and FOLFOX: patients should have had only 1 prior chemotherapy regimen for the metastatic setting, consisting of 1L fluoropyrimidine-irinotecan-based chemotherapy ± bevacizumab.
4. A baseline new tumor sample (formalin-fixed paraffin-embedded [FFPE] core needle biopsy) from a metastatic or primary site. If the patient has an available tumor sample as an FFPE block with sufficient material (at least 20 slides with >20% tumor content) and has not received further anticancer treatment since sample collection, then a new tumor biopsy at baseline is not necessary. Archival FFPE slides are not acceptable. Archival tumor material (ie, FFPE block) from before the last line of treatment received is only acceptable if the patient has not been treated with anti-human epidermal growth factor receptor-2 (HER-2) or anti EGFR (3L+ mCRC only) therapies, but should be confirmed by the Sponsor.
5. Amenable for biopsy (if safe/feasible)
6. Measurable disease as defined by RECIST v1.1 by radiologic methods
7. ECOG PS of 0 or 1
8. Life expectancy >=12 weeks, as per investigator
9. Left ventricular ejection fraction (LVEF) >=50% by echocardiogram (ECHO) or multigated acquisition scan (MUGA)
10. Adequate organ function:
• ANC >=1.5 X 109/L
• Hemoglobin >=9 g/dL
• Platelets >=100 x 109/L
• Serum magnesium, sodium, corrected total calcium, phosphate, and potassium within normal ranges (or corrected with supplements or appropriate treatment).
• Alanine aminotransferase (ALT), aspartate aminotransferase (AST) <=2.5 x upper limit of normal (ULN) and total bilirubin <=1.5 x ULN (unless due to known Gilbert*s syndrome who are excluded if total bilirubin >3.0 x ULN or direct bilirubin >1.5 x ULN); in cases of liver involvement, ALT/AST <=5 x ULN and total bilirubin <=1.5 x ULN will be allowed, unless due to known Gilbert*s syndrome when total bilirubin <=3.0 x ULN or direct bilirubin <=1.5 x ULN will be allowed.

• Serum creatinine <=1.5 x ULN or creatinine clearance (CrCl) >=60 mL/min calculated according to the Cockroft and Gault formula or Modification of Diet in Renal Disease (MDRD) formula for patients aged >65 years (Appendix 2, Section 20.2)
• Serum albumin >=3 g/dL
• International normalized ratio (INR) or prothrombin time (PT) <=1.5 x ULN unless patient is receiving anticoagulant therapy and in therapeutic range of intended used anticoagulant
• Activated partial thromboplastin time (APTT) or partial thromboplastin time (PTT) <=1.5 x ULN unless patient is receiving anticoagulant therapy and is in therapeutic range of intended used anticoagulant
11. Willing to undergo testing for human immunodeficiency virus (HIV) if not tested within the past 6 months. Known HIV-positive patients are eligible provided the cluster of differentiation 4 (CD4+) PROPERTY OF MERUS N.V. CONFIDENTIAL Page 94 of 166
count is >=300/µL, viral load is undetectable, and the patient is currently receiving highly active antiretroviral therapy (HAART).

Exclusion criteria

1. Central nervous system metastases that are untreated or symptomatic, or require radiation, surgery, or continued steroid therapy to control symptoms within 14 days of study entry
2. Known leptomeningeal involvement
3. Participation in another clinical trial or treatment with any investigational drug within 4 weeks prior to study entry
4. Any systemic anticancer therapy within 4 weeks or 5 half-lives, whichever is shorter, of the first dose of study treatment. For cytotoxic agents that have major delayed toxicity (eg, mitomycin C, nitrosoureas), or anticancer immunotherapies, a washout period of 6 weeks is required.
5. Requirement for immunosuppressive medication (eg, methotrexate, cyclophosphamide)
6. Major surgery or radiotherapy within 3 weeks of the first dose of study treatment. Patients who received prior radiotherapy to >=25% of bone marrow are not eligible, irrespective of when it was received.
7. Persistent Grade >1 clinically significant toxicities related to prior antineoplastic therapies (except for alopecia); stable sensory neuropathy Grade <=2 National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03 is allowed.
8. History of hypersensitivity reaction to any of the excipients of petosemtamab, human proteins, or any non-IMP treatment required for this study
9. Uncontrolled hypertension (systolic BP >150 mmHg and/or diastolic BP >100 mmHg) with appropriate treatment; unstable angina; history of congestive heart failure of Class II-IV New York Heart Association (NYHA) criteria, or serious cardiac arrhythmia requiring treatment (except atrial fibrillation, paroxysmal

supraventricular tachycardia); or history of myocardial infarction within 6 months of study entry
10. History of prior malignancies with the exception of excised cervical intraepithelial neoplasia or nonmelanoma skin cancer, or curatively treated cancer deemed at low risk for recurrence with no evidence of disease for >=3 years.
11. Current dyspnea at rest of any origin, or other diseases requiring continuous oxygen therapy, including patients with a history of ILD (eg, pneumonitis or pulmonary fibrosis), or evidence of ILD on baseline chest computerized tomography (CT) scan
12. Current serious illness or medical conditions including, but not limited to, uncontrolled active infection, clinically significant pulmonary, metabolic, or psychiatric disorders
13. Patients with known infectious diseases:
• Active hepatitis B infection (hepatitis B surface antigen [HbsAg] positive) without receiving antiviral treatment. Note:
o Patients who are HbsAg positive must receive antiviral treatment with lamivudine, tenofovir, entecavir, or other antiviral agents, starting at least >=7 days before the initiation of study treatment.
o Patients with antecedents of hepatitis B (eg, anti-hepatitis B core (anti-HBc) positive, HbsAg, and hepatitis B virus [HBV]-DNA negative) are eligible.
• Positive test for hepatitis C virus (HCV) RNA. Note: Patients in whom HCV infection resolved spontaneously (ie, positive HCV antibodies without detectable HCV RNA), or who achieved a sustained response after antiviral treatment and show absence of detectable HCV RNA >=6 months (with the use of interferon [IFN]-free regimens) or >=12 months (with the use of IFN-based regimens) after cessation of antiviral treatment, are eligible.
14. Pregnant or breastfeeding patients; patients of childbearing potential must use highly effective contraception methods prior to study entry, for the duration of study participation, and for 6 months after the last dose of petosemtamab.
15. 1L HNSCC combination cohort: has a diagnosis of immunodeficiency, or is receiving systemic steroid therapy or any form of immunosuppressive therapy within 7 days prior to the first dose. Corticosteroids used as premedication for allergic reactions or IRRs specified in the protocol are allowed.
16. 1L HNSCC combination cohort: active autoimmune disease that has required systemic immune suppressive treatment in the past 2 years; replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered immune suppressive treatment.
17. 1L HNSCC combination cohort: has had an allogeneic tissue/solid organ transplant
18. 1L HNSCC combination or HNSCC single-agent cohort: patients may not have a primary tumor site of nasopharynx (any histology)
19. Patients previously treated with anti-EGFR inhibitors are not eligible for this study (except in 3L+ mCRC, see Inclusion Criterion [IC] 3).

20. mCRC cohorts: mCRC with a RAS/RAF mutation identified by local ctDNA or tumor test at screening, or identified as such in disease history, are not eligible for this study.
21. 2L mCRC cohorts: Patients with an active inflammatory bowel disease, or other bowel disease causing chronic diarrhea (defined as NCI-CTCAE Grade >=2), are not eligible for this study.
22. 2L mCRC cohorts: Patients with peripheral sensory neuropathy with functional impairment (defined as NCI-CTCAE Grade >=3) are not eligible for this study.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	25-05-2023
Enrollment:	34
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Petosemtamab
Generic name:	MCLA-158

Ethics review

Approved WMO

Date:	19-04-2022

Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	24-10-2022
Application type:	First submission
Review commission:	METC NedMec (Utrecht)
Approved WMO Date:	16-02-2023
Application type:	Amendment
Review commission:	METC NedMec (Utrecht)
Approved WMO Date:	15-03-2023
Application type:	Amendment
Review commission:	METC NedMec (Utrecht)
Approved WMO Date:	30-03-2023
Application type:	Amendment
Review commission:	METC NedMec (Utrecht)
Approved WMO Date:	22-05-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-06-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-07-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-07-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-07-2024

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-07-2024
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-513627-16-01
EudraCT	EUCTR2017-004745-24-NL
ClinicalTrials.gov	NCT03526835
CCMO	NL81045.041.22