Clinical Trial Protocol

# 1. Title

Protocol Title

Phase 2 Study of Amivantamab in Patients with Advanced Colorectal Cancer with EGFR and MET Alterations

Background & Rationale

Colorectal cancer is a significant cause of cancer-related deaths worldwide. For patients with advanced-stage disease, particularly those with alterations in the epidermal growth factor receptor (EGFR) and the hepatocyte growth factor receptor (MET) pathways, treatment options are limited and often ineffective. Amivantamab, a novel bispecific antibody that targets both EGFR and MET, has shown promise in treating non-small cell lung cancer (NSCLC). This Phase 2 study is designed to investigate the safety and efficacy of amivantamab in a similar cohort of patients with advanced colorectal cancer.

Study Objectives

Primary Objective  
• To determine the objective response rate (ORR) of amivantamab in patients with documented EGFR and MET alterations in advanced colorectal cancer.

Secondary Objectives  
• To evaluate the progression-free survival (PFS) of patients treated with amivantamab.  
• To assess the overall survival (OS) of the study population.  
• To determine the disease control rate (DCR) in patients receiving amivantamab.  
• To characterize the safety profile of amivantamab in this patient population.

Study Design

This is a single-arm, open-label, Phase 2 clinical trial evaluating the efficacy and safety of amivantamab in patients with advanced colorectal cancer harboring EGFR and MET alterations.

Key Inclusion Criteria  
• Adult patients (≥18 years of age) diagnosed with advanced or metastatic colorectal cancer.  
• Molecularly confirmed EGFR and MET pathway alterations.  
• Disease progression following standard therapy, or patients for whom no standard treatments are available.

Treatment Plan

Eligible patients will be administered amivantamab intravenously at the recommended Phase 2 dose on Day 1 of each 21-day cycle. Dose adjustments will be made according to individual patient tolerance.

Study Endpoints

Primary Endpoint  
• Objective response rate (ORR) as measured by RECIST v1.1 criteria.

Secondary Endpoints  
• Progression-free survival (PFS).  
• Overall survival (OS).  
• Disease control rate (DCR).  
• Incidence and severity of adverse events (AEs).

Statistical Considerations

The study will enroll approximately 100 patients to ensure sufficient power to detect a clinically meaningful difference in ORR. Secondary endpoints will include survival analyses for PFS and OS.

Timeline

The estimated duration of the study is 24 months, starting from patient enrollment to the completion of final data analysis.

# 2. Background

Background & Rationale

Colorectal cancer (CRC) remains a significant public health challenge as one of the leading causes of cancer-related mortality globally. The prognosis for patients with advanced-stage CRC is particularly poor, with a limited repertoire of effective treatment options. This is especially true for patients whose tumors harbor alterations in the epidermal growth factor receptor (EGFR) and the hepatocyte growth factor receptor (MET) pathways. These genetic aberrations are associated with aggressive tumor behavior and poor response to conventional therapies.

Amivantamab is a first-in-class, fully human bispecific antibody that simultaneously targets EGFR and MET receptors. By binding to these two critical pathways, amivantamab is designed to inhibit tumor growth and survival. The clinical utility of amivantamab has been previously established in non-small cell lung cancer (NSCLC), where it has demonstrated efficacy in patients with EGFR exon 20 insertion mutations, a subgroup known for its resistance to other EGFR-targeted therapies.

Given the success of amivantamab in NSCLC, there is a compelling rationale to explore its therapeutic potential in CRC. This Phase 2 study is predicated on the hypothesis that amivantamab's dual inhibition of EGFR and MET may provide clinical benefit to patients with advanced CRC harboring alterations in these pathways. The study will evaluate the safety and efficacy of amivantamab in this new setting, with the hope of expanding the treatment landscape for these patients.

The investigation into amivantamab's activity in CRC is timely and significant, as it may address an unmet medical need by providing a targeted therapy option for a patient population with limited treatment alternatives. The study's outcomes have the potential to inform future research and therapeutic strategies, ultimately improving survival and quality of life for patients with advanced CRC.

# 3. Objectives

Objectives

Primary Objective  
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Secondary Objectives  
• To evaluate the progression-free survival (PFS) of patients treated with amivantamab.  
• To assess the overall survival (OS) of the study population.  
• To determine the disease control rate (DCR) in patients receiving amivantamab.  
• To characterize the safety profile of amivantamab in this patient population.

# 4. Study Design

Study Design

Overview  
This clinical trial is a single-arm, open-label, Phase 2 study designed to assess the safety and efficacy of amivantamab in patients with advanced colorectal cancer (CRC) who have documented alterations in the epidermal growth factor receptor (EGFR) and the hepatocyte growth factor receptor (MET) pathways.

Study Population  
The study will enroll adult patients (≥18 years of age) diagnosed with advanced or metastatic CRC. Eligible participants must have molecularly confirmed EGFR and MET pathway alterations and must have experienced disease progression following standard therapy or have no available standard treatment options.

Intervention  
Participants will receive amivantamab administered intravenously at the recommended Phase 2 dose. The administration will occur on Day 1 of each 21-day cycle. Dose adjustments will be made based on patient tolerance to the treatment.

Duration of Treatment  
Treatment will continue until disease progression, unacceptable toxicity, withdrawal of consent, or other criteria for discontinuation are met, as per the study protocol.

Study Assessments  
Tumor assessments will be conducted using RECIST v1.1 criteria at baseline and at specified intervals throughout the study to evaluate the primary and secondary endpoints. Safety assessments, including the monitoring of adverse events, will be conducted throughout the study period.

Study Endpoints  
The primary endpoint of the study is the objective response rate (ORR), while secondary endpoints include progression-free survival (PFS), overall survival (OS), disease control rate (DCR), and the safety profile of amivantamab.

Statistical Analysis  
The study aims to enroll approximately 100 patients to ensure adequate power to detect a clinically meaningful ORR. Secondary analyses will focus on survival endpoints such as PFS and OS.

Study Duration  
The estimated duration of the study is 24 months, which includes patient enrollment, treatment, follow-up, and final data analysis.

Ethical Considerations  
The study will be conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines, and all applicable regulatory requirements. An independent ethics committee or institutional review board will approve the study protocol before initiation. Informed consent will be obtained from all participants before enrollment in the study.

# 5. Population

5. Population

5.1 Study Population

The study will recruit adult patients (≥18 years of age) diagnosed with advanced or metastatic colorectal cancer (CRC). To be eligible, participants must have molecularly confirmed alterations in both the epidermal growth factor receptor (EGFR) and the hepatocyte growth factor receptor (MET) pathways. These alterations are critical inclusion criteria as they are the targets of the investigational drug, amivantamab.

5.2 Inclusion Criteria

1. Age: Participants must be 18 years of age or older.  
2. Diagnosis: Patients must have a histologically or cytologically confirmed diagnosis of advanced or metastatic CRC.  
3. Genetic Alterations: Patients must have documented alterations in EGFR and MET pathways, as confirmed by a validated molecular assay.  
4. Disease Status: Participants must have experienced disease progression following standard therapy or be considered unsuitable for existing standard treatment options.  
5. Prior Therapy: Patients must have recovered from the acute adverse effects of any prior anti-cancer therapy, and a specified time must have elapsed since the completion of the last therapy.  
6. Performance Status: Participants must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.  
7. Organ Function: Adequate bone marrow, liver, and renal function as defined by protocol-specific laboratory criteria.

5.3 Exclusion Criteria

1. Prior Treatment: Patients who have received previous treatment with an EGFR or MET inhibitor.  
2. Concurrent Conditions: Presence of any serious or uncontrolled medical disorder, active infection, or uncontrolled intercurrent illness.  
3. Brain Metastases: Patients with symptomatic, untreated, or unstable central nervous system (CNS) metastases.  
4. Pregnancy: Pregnant or breastfeeding women, or women and men of reproductive potential not willing to employ effective birth control.  
5. Allergies: Known hypersensitivity to any component of amivantamab or similar compounds.  
6. Other Therapies: Participation in another clinical study with an investigational product during the last 30 days.

5.4 Screening and Enrollment

Potential participants will undergo a screening process to confirm eligibility, including but not limited to medical history, physical examination, performance status evaluation, laboratory tests, and molecular profiling. Upon meeting all inclusion and none of the exclusion criteria, eligible patients will be enrolled in the study.

5.5 Withdrawal Criteria

Participants may be withdrawn from the study for reasons including, but not limited to, disease progression, unacceptable toxicity, non-compliance with study protocol, withdrawal of consent, or at the discretion of the investigator. Specific criteria for treatment discontinuation will be detailed in the study protocol.

5.6 Sample Size

The study aims to enroll approximately 100 patients. This sample size is calculated to provide adequate power to detect a clinically meaningful objective response rate (ORR), with secondary analyses for progression-free survival (PFS) and overall survival (OS).

# 6. Procedures

6. Procedures

6.1 Treatment Administration

Patients will receive amivantamab administered intravenously at the recommended Phase 2 dose. The initial dose will be given on Day 1 of each 21-day cycle. Subsequent doses may be adjusted based on individual patient tolerance and in accordance with predefined dose modification criteria. Treatment will continue until disease progression, unacceptable toxicity, withdrawal of consent, or other discontinuation criteria are met.

6.2 Dose Modification

Dose modifications for amivantamab will be guided by the severity and type of adverse events experienced by the patient. The protocol will include specific instructions for dose reductions, interruptions, and discontinuation related to adverse event management.

6.3 Concomitant Medications

The use of concomitant medications will be allowed as necessary for the management of comorbid conditions and treatment-related adverse events, provided they do not interfere with the study drug's mechanism of action or the interpretation of study results. Prohibited medications will include other investigational drugs and treatments known to interact with EGFR or MET pathways.

6.4 Assessment Schedule

Patients will undergo regular assessments to monitor the efficacy and safety of the treatment. These will include:  
• Baseline evaluations prior to the first dose of amivantamab.  
• Tumor assessments using RECIST v1.1 criteria at baseline, every two cycles (6 weeks), and at treatment discontinuation.  
• Safety assessments, including physical examinations, vital signs, laboratory tests, and adverse event monitoring, will occur at each visit.  
• Imaging studies as needed to confirm responses or progression.

6.5 Criteria for Discontinuation

Patients may be discontinued from treatment for reasons including:  
• Disease progression as defined by RECIST v1.1 criteria.  
• Occurrence of unacceptable toxicity not manageable with dose modification.  
• Patient withdrawal of consent.  
• Non-compliance with the study protocol.  
• Investigator's judgment that discontinuation is in the patient's best interest.

6.6 Post-Treatment Follow-Up

Upon discontinuation of treatment, patients will enter a post-treatment follow-up phase to monitor for late-emerging adverse events and to collect survival data. Follow-up visits will include:  
• A safety follow-up visit 30 days after the last dose of amivantamab.  
• Survival status assessments every 3 months until the end of the study or patient death.

6.7 Data Collection and Management

Data will be collected using electronic case report forms (eCRFs). All data will be handled confidentially and analyzed in accordance with the study's statistical analysis plan. Data management will be conducted by a designated team to ensure accuracy and compliance with regulatory standards.

6.8 Quality Assurance

The study will implement quality assurance measures including site monitoring, data audits, and regular review meetings to ensure adherence to the protocol and Good Clinical Practice (GCP) guidelines. Any protocol deviations will be documented and addressed promptly.

# 7. Statistical Analysis

7. Statistical Analysis

7.1 General Considerations

The statistical analysis of this Phase 2 study will be performed according to the principles of the International Conference on Harmonisation (ICH) E6 Guidelines for Good Clinical Practice. All statistical tests will be two-sided and will be conducted at a 5% significance level unless otherwise specified.

7.2 Analysis Populations

The analysis populations will include:  
• Intent-to-Treat (ITT) Population: All patients who receive at least one dose of amivantamab and have documented EGFR and MET alterations.  
• Safety Population: All patients who receive at least one dose of amivantamab, with adverse events summarized by frequency and severity.  
• Per-Protocol Population: Patients who complete the study without significant protocol deviations that could impact the efficacy or safety assessment.

7.3 Primary Efficacy Analysis

The primary efficacy endpoint, the objective response rate (ORR), will be calculated as the proportion of patients who achieve a complete response (CR) or partial response (PR) as per RECIST v1.1 criteria. The exact binomial method will be used to construct 95% confidence intervals (CIs) around the ORR estimate.

7.4 Secondary Efficacy Analysis

Secondary efficacy endpoints, including progression-free survival (PFS) and overall survival (OS), will be analyzed using Kaplan-Meier methods. Median PFS and OS will be estimated with corresponding 95% CIs. The log-rank test will be used to compare survival distributions if appropriate.

The disease control rate (DCR) will be calculated as the proportion of patients who achieve CR, PR, or stable disease (SD) for a specified time period. The exact binomial method will be used to calculate 95% CIs for the DCR.

7.5 Safety Analysis

Adverse events (AEs) will be summarized using descriptive statistics. The incidence of AEs will be tabulated by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA). The severity of AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).

7.6 Interim Analysis

An interim analysis may be planned to assess safety and futility. The criteria for stopping the study for safety or futility will be predefined in the study protocol. The interim analysis will be conducted by an independent data monitoring committee (IDMC).

7.7 Sample Size Justification

The sample size of 100 patients is based on assumptions about the expected ORR and the precision of the estimate required. The study is powered to detect a clinically meaningful ORR with adequate precision to estimate the 95% CI. Power calculations and assumptions will be detailed in the statistical analysis plan (SAP).

7.8 Data Management and Monitoring

Data will be collected and managed using electronic data capture systems. Data quality will be ensured through regular monitoring, validation checks, and audits. All protocol deviations will be recorded and analyzed to assess their impact on the study's integrity.

7.9 Statistical Software

All statistical analyses will be performed using the latest version of a statistical software package validated for clinical trial analysis, such as SAS or R.

7.10 Reporting of Results

The results of the statistical analyses will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines for clinical trials. The final study report will include detailed statistical methodology and the results of all primary and secondary analyses.

7.11 Statistical Analysis Plan (SAP)

A detailed SAP will be developed prior to the commencement of the study and will be finalized before the database lock. The SAP will outline the detailed statistical methods for the analysis of primary and secondary endpoints, handling of missing data, multiplicity adjustments, and subgroup analyses.

# 8. Safety

8. Safety

8.1 Safety Monitoring

Safety monitoring will be a continuous process throughout the study, with regular assessments at each patient visit. Adverse events (AEs) will be recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.

8.2 Reporting of Adverse Events

All AEs, regardless of severity or causality, will be reported by the study investigators. Serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs) will be reported to the regulatory authorities, ethics committees, and the sponsor according to local regulations and the study protocol.

8.3 Management of Adverse Events

The study protocol will include detailed guidelines for the management of AEs, including dose modifications, treatment interruptions, and discontinuation criteria. The primary concern will be patient safety, and decisions will be made in the best interest of the patient.

8.4 Data Safety Monitoring Board (DSMB)

An independent Data Safety Monitoring Board (DSMB) will be established to periodically review safety data and provide recommendations on the continuation, modification, or termination of the study based on safety considerations.

8.5 Criteria for Discontinuation due to Adverse Events

Patients may be discontinued from treatment due to AEs if they experience:  
• Grade 4 hematologic toxicity lasting more than 7 days or Grade 4 non-hematologic toxicity.  
• Any Grade 3 or 4 toxicity that does not resolve to Grade 1 or baseline within 2 weeks.  
• Any life-threatening or disabling AE.  
• Any AE that, in the opinion of the investigator, poses a significant risk to the patient's health or compromises the study's integrity.

8.6 Safety Endpoints

The safety endpoints of the study will include:  
• Incidence and severity of AEs and SAEs.  
• Changes in laboratory values and vital signs.  
• Dose interruptions, reductions, and treatment discontinuations due to AEs.

8.7 Long-term Safety Follow-up

Patients will be followed for safety for 30 days after the last dose of amivantamab. Any late-emerging AEs or SAEs will be recorded and reported as per the study protocol.

8.8 Safety Analysis

The safety population will include all patients who receive at least one dose of amivantamab. Safety data will be summarized using descriptive statistics, with AEs tabulated by frequency, severity, and relationship to the study drug.

8.9 Safety Reporting to Regulatory Authorities

All SAEs and SUSARs will be reported to the appropriate regulatory authorities within the timelines specified by local regulations. Annual safety reports will be submitted to regulatory authorities and ethics committees as required.

8.10 Patient Education and Informed Consent

Patients will be educated about the potential risks and AEs associated with amivantamab. Informed consent will be obtained from all patients, which will include a discussion of the study's safety monitoring and the patient's right to withdraw from the study at any time due to safety concerns.

8.11 Emergency Unblinding

In the event of a medical emergency where knowledge of the study treatment is essential for patient care, procedures for unblinding will be followed as per the study protocol.

8.12 Record Keeping and Documentation

All safety-related information will be documented in the patient's medical records and in the study case report forms (CRFs). Documentation will include details of the AE, interventions, outcomes, and any follow-up actions taken.

8.13 Training

All study personnel will be trained on the protocol's safety procedures, including the recognition and reporting of AEs and SAEs, to ensure accurate and timely collection of safety data.