Clinical Trial Protocol

# 1. Title

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

Background & Rationale

Colorectal cancer is a leading cause of cancer-related mortality worldwide. The prognosis for patients with advanced-stage colorectal cancer is poor, with limited treatment options available once standard therapies have failed. Alterations in the epidermal growth factor receptor (EGFR) and the mesenchymal-epithelial transition (MET) pathways are implicated in the progression and resistance to treatment in colorectal cancer. Amivantamab is a novel bispecific antibody that simultaneously targets both EGFR and MET receptors and has shown promising results in non-small cell lung cancer (NSCLC). This Phase 2 study is designed to explore the therapeutic potential of amivantamab in advanced colorectal cancer patients with EGFR and MET alterations.

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 patients treated with amivantamab.  
• To determine the disease control rate (DCR) in the study population.  
• To characterize the safety and tolerability profile of amivantamab in this patient cohort.

Study Design

This is a single-arm, open-label, Phase 2 study designed to assess the efficacy and safety of amivantamab in patients with advanced colorectal cancer with specific genetic alterations in EGFR and MET.

Key Inclusion Criteria  
• Patients must be adults aged 18 years or older with a diagnosis of advanced or metastatic colorectal cancer.  
• There must be documented evidence of EGFR and MET pathway alterations in the tumor tissue.  
• Patients should have experienced disease progression on or after standard therapy, or be considered unsuitable for existing standard treatment options.

Treatment Plan

Eligible patients will receive amivantamab administered intravenously at the recommended Phase 2 dose on Day 1 of each 21-day cycle. Dose adjustments will be made according to patient tolerance and in response to any observed adverse events.

Study Endpoints

Primary Endpoint  
• Objective response rate (ORR), defined as the proportion of patients with a partial or complete response to treatment.

Secondary Endpoints  
• Progression-free survival (PFS), the time from treatment initiation to disease progression or death from any cause.  
• Overall survival (OS), the time from treatment initiation to death from any cause.  
• Disease control rate (DCR), the proportion of patients with a complete response, partial response, or stable disease.  
• Incidence and severity of adverse events as a measure of the safety and tolerability of amivantamab.

Statistical Considerations

The study will enroll approximately 100 patients to ensure sufficient power to detect a clinically meaningful difference in the primary endpoint of ORR. Secondary endpoints will be analyzed to provide additional efficacy and safety data.

Timeline

The estimated duration of the study is 24 months, which includes the time from the start of patient enrollment to the completion of final data analysis.

# 2. Background

Background & Rationale

Colorectal cancer is a leading cause of cancer-related mortality worldwide. The prognosis for patients with advanced-stage colorectal cancer is poor, with limited treatment options available once standard therapies have failed. Alterations in the epidermal growth factor receptor (EGFR) and the mesenchymal-epithelial transition (MET) pathways are implicated in the progression and resistance to treatment in colorectal cancer. These alterations can lead to uncontrolled cell growth, invasion, and metastasis, contributing to the aggressive nature of the disease and poor outcomes in patients.

Amivantamab is a novel bispecific antibody that simultaneously targets both EGFR and MET receptors. By inhibiting these pathways, amivantamab has the potential to impede tumor growth and overcome resistance mechanisms. The efficacy of amivantamab has been demonstrated in non-small cell lung cancer (NSCLC), a cancer type known for EGFR alterations, suggesting that it may also be effective in other EGFR-driven cancers, such as colorectal cancer.

Given the unmet medical need for effective treatments in advanced colorectal cancer with EGFR and MET alterations, this Phase 2 study is designed to explore the therapeutic potential of amivantamab in this patient population. The study will assess the safety and efficacy of amivantamab, with the aim of providing a new treatment option that could improve clinical outcomes for these patients.

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 patients treated with amivantamab.  
• To determine the disease control rate (DCR) in the study population.  
• To characterize the safety and tolerability profile of amivantamab in this patient cohort.

Study Design

This is a single-arm, open-label, Phase 2 study designed to assess the efficacy and safety of amivantamab in patients with advanced colorectal cancer with specific genetic alterations in EGFR and MET.

Key Inclusion Criteria  
• Patients must be adults aged 18 years or older with a diagnosis of advanced or metastatic colorectal cancer.  
• There must be documented evidence of EGFR and MET pathway alterations in the tumor tissue.  
• Patients should have experienced disease progression on or after standard therapy, or be considered unsuitable for existing standard treatment options.

Treatment Plan

Eligible patients will receive amivantamab administered intravenously at the recommended Phase 2 dose on Day 1 of each 21-day cycle. Dose adjustments will be made according to patient tolerance and in response to any observed adverse events.

Study Endpoints

Primary Endpoint  
• Objective response rate (ORR), defined as the proportion of patients with a partial or complete response to treatment.

Secondary Endpoints  
• Progression-free survival (PFS), the time from treatment initiation to disease progression or death from any cause.  
• Overall survival (OS), the time from treatment initiation to death from any cause.  
• Disease control rate (DCR), the proportion of patients with a complete response, partial response, or stable disease.  
• Incidence and severity of adverse events as a measure of the safety and tolerability of amivantamab.

Statistical Considerations

The study will enroll approximately 100 patients to ensure sufficient power to detect a clinically meaningful difference in the primary endpoint of ORR. Secondary endpoints will be analyzed to provide additional efficacy and safety data.

Timeline

The estimated duration of the study is 24 months, which includes the time from the start of patient enrollment to the completion of final data analysis.

# 3. Objectives

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 patients treated with amivantamab.  
• To determine the disease control rate (DCR) in the study population.  
• To characterize the safety and tolerability profile of amivantamab in this patient cohort.

# 4. Study Design

Study Design

Overview  
This clinical trial is a single-arm, open-label, Phase 2 study that aims to evaluate the efficacy and safety of amivantamab in patients with advanced colorectal cancer harboring specific genetic alterations in the EGFR and MET pathways.

Study Population  
The study will enroll approximately 100 adult patients (aged 18 years or older) diagnosed with advanced or metastatic colorectal cancer. All participants must have documented EGFR and MET pathway alterations and should have experienced disease progression following standard therapy or be deemed unsuitable for existing standard treatment options.

Intervention  
Eligible patients will be administered amivantamab 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 and in response to any adverse events observed.

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

Study Assessments  
Efficacy assessments will include measurement of tumor size and response using appropriate imaging techniques, in accordance with RECIST (Response Evaluation Criteria in Solid Tumors) guidelines. Safety assessments will include monitoring and recording all adverse events, routine laboratory tests, vital signs, and physical examinations.

Study Endpoints  
The primary endpoint of the study is the objective response rate (ORR), defined as the proportion of patients with a partial or complete response to treatment. Secondary endpoints include progression-free survival (PFS), overall survival (OS), disease control rate (DCR), and the incidence and severity of adverse events.

Statistical Analysis  
The sample size of 100 patients is calculated to provide adequate statistical power to detect a clinically meaningful improvement in the primary endpoint of ORR. Secondary endpoints will be analyzed to provide additional information on the efficacy and safety of amivantamab.

Study Duration  
The total estimated study duration is 24 months, which includes patient enrollment, treatment, follow-up, and final data analysis. The study timeline may be adjusted based on actual enrollment rates and other factors that could influence the duration of the study.

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 prior to enrollment in the study.

# 5. Population

5. POPULATION

5.1 Study Population

The study will enroll approximately 100 adult patients (aged 18 years or older) diagnosed with advanced or metastatic colorectal cancer. All participants must have documented EGFR and MET pathway alterations and should have experienced disease progression following standard therapy or be deemed unsuitable for existing standard treatment options.

5.2 Inclusion Criteria

1. Patients must be adults aged 18 years or older.  
2. Histologically or cytologically confirmed diagnosis of advanced or metastatic colorectal cancer.  
3. Documented evidence of EGFR and MET pathway alterations in the tumor tissue.  
4. Disease progression on or after standard therapy, or patients considered unsuitable for existing standard treatment options.  
5. Adequate organ function as defined by study-specific laboratory tests.  
6. ECOG (Eastern Cooperative Oncology Group) performance status of 0-1.  
7. Life expectancy of at least 3 months.  
8. Ability to understand and willingness to sign a written informed consent document.

5.3 Exclusion Criteria

1. Prior treatment with any drug specifically targeting EGFR and MET pathways.  
2. Known hypersensitivity to any component of amivantamab or similar compounds.  
3. Active brain metastases or leptomeningeal metastases.  
4. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.  
5. Pregnant or breastfeeding women, or women of childbearing potential not using effective contraception.  
6. Any other medical conditions or use of medications that, in the opinion of the investigator, would make the patient unsuitable for enrollment or could interfere with the patient participating in or completing the study.

5.4 Withdrawal Criteria

Patients may withdraw from the study at any time for any reason. Additionally, the following criteria will be used for withdrawal from the study treatment:

1. Disease progression as defined by RECIST guidelines.  
2. Unacceptable adverse event(s).  
3. Intercurrent illness that prevents further administration of treatment.  
4. Noncompliance with trial treatment or procedure requirements.  
5. Administrative reasons requiring withdrawal from the trial (e.g., loss to follow-up).  
6. Decision by the patient to discontinue treatment.  
7. Any changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator.

5.5 Replacement of Participants

Participants who withdraw from the study before completion of the protocol-specified treatment period will be replaced to ensure that the study maintains the planned sample size of 100 patients. This will allow for adequate statistical power to detect a clinically meaningful difference in the primary endpoint of ORR.

# 6. Procedures

6. PROCEDURES

6.1 Screening and Enrollment

6.1.1 Initial Screening  
• Review of medical history and previous treatments.  
• Confirmation of advanced or metastatic colorectal cancer diagnosis.  
• Documentation of EGFR and MET pathway alterations.  
• Assessment of organ function through laboratory tests.  
• Evaluation of ECOG performance status.  
• Pregnancy test for women of childbearing potential.

6.1.2 Informed Consent  
• Provision of study information to potential participants.  
• Discussion of potential risks and benefits.  
• Obtaining written informed consent from participants.

6.1.3 Enrollment  
• Assignment of unique participant identification number.  
• Scheduling of baseline assessments and treatment initiation.

6.2 Treatment Administration

6.2.1 Dosing Schedule  
• Administration of intravenous amivantamab at the recommended Phase 2 dose.  
• Treatment on Day 1 of each 21-day cycle.

6.2.2 Dose Adjustments  
• Monitoring for adverse events and tolerability.  
• Adjustment of amivantamab dose as necessary based on patient response and side effects.

6.3 Efficacy Assessments

6.3.1 Tumor Evaluation  
• Imaging studies to measure tumor size and response as per RECIST guidelines.  
• Frequency of assessments as per protocol schedule.

6.3.2 Response Criteria  
• Determination of partial or complete response, stable disease, or disease progression.

6.4 Safety Assessments

6.4.1 Adverse Event Monitoring  
• Continuous monitoring and documentation of adverse events.  
• Severity grading of adverse events according to CTCAE (Common Terminology Criteria for Adverse Events).

6.4.2 Routine Monitoring  
• Regular laboratory tests including hematology, biochemistry, and urinalysis.  
• Vital signs and physical examination at specified intervals.

6.5 Study Endpoints

6.5.1 Primary Endpoint  
• Objective response rate (ORR) assessed at defined time points.

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

6.6 Follow-Up

6.6.1 Post-Treatment Follow-Up  
• Post-treatment monitoring for late-emerging adverse events.  
• Follow-up imaging studies to assess disease status.

6.6.2 Survival Follow-Up  
• Periodic updates on survival status for all participants.

6.7 Study Discontinuation/Withdrawal

6.7.1 Criteria for Discontinuation  
• Disease progression as per RECIST.  
• Unacceptable toxicity or adverse events.  
• Withdrawal of consent by the participant.  
• Non-compliance with study protocol.  
• Administrative or other reasons as determined by the study team.

6.7.2 Procedures for Discontinuation  
• Final assessment and documentation of reason for discontinuation.  
• Post-discontinuation follow-up for safety as per protocol.

6.8 Data Collection and Management

6.8.1 Data Collection  
• Collection of efficacy and safety data using case report forms (CRFs).  
• Documentation of all protocol-required information.

6.8.2 Data Management  
• Entry and verification of data in the study database.  
• Maintenance of data confidentiality and participant privacy.

6.9 Statistical Analysis Plan

6.9.1 Analysis Populations  
• Definition of intent-to-treat (ITT) and per-protocol (PP) populations for analyses.

6.9.2 Analysis Methods  
• Description of statistical methods for primary and secondary endpoints.  
• Use of appropriate statistical tests for comparison and inference.

6.9.3 Interim Analysis  
• Potential for interim analysis for safety and efficacy as per predefined criteria.

6.9.4 Final Analysis  
• Comprehensive analysis upon completion of the study to assess primary and secondary endpoints.

6.10 Quality Assurance

6.10.1 Monitoring  
• Regular monitoring visits to ensure compliance with the protocol.  
• Verification of informed consent, eligibility, and data accuracy.

6.10.2 Audits  
• Periodic audits to review study conduct and regulatory compliance.

6.10.3 Protocol Deviations  
• Documentation and reporting of protocol deviations.  
• Assessment of impact on study integrity and participant safety.

# 7. Statistical Analysis

6.9 STATISTICAL ANALYSIS PLAN

6.9.1 Analysis Populations

Intent-to-Treat Population  
The intent-to-treat (ITT) population will include all patients who receive at least one dose of amivantamab. All randomized patients will be included in the ITT population for efficacy analyses, regardless of protocol adherence or subsequent withdrawal from the study.

Per-Protocol Population  
The per-protocol (PP) population will consist of patients who complete the study without any significant protocol deviations that could impact the efficacy assessment. This population will be used for sensitivity analyses.

6.9.2 Analysis Methods

Primary Efficacy Analysis  
The primary efficacy endpoint, objective response rate (ORR), will be calculated as the proportion of patients achieving a complete or partial response, as defined by RECIST criteria. The exact binomial method will be used to calculate 95% confidence intervals for the ORR.

Secondary Efficacy Analysis  
Secondary endpoints, including progression-free survival (PFS), overall survival (OS), and disease control rate (DCR), will be analyzed using Kaplan-Meier methods. Median times to events with 95% confidence intervals will be estimated. The log-rank test will be used to compare survival distributions if applicable.

Safety Analysis  
Adverse events will be summarized using frequencies and percentages. The severity of adverse events will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE). Summary statistics will be provided for laboratory measurements and vital signs.

Subgroup Analysis  
Subgroup analyses will be conducted to explore the consistency of the treatment effect across various patient subgroups, such as age, sex, baseline performance status, and molecular alterations.

Interim Analysis  
An interim analysis may be conducted for safety and efficacy after a predetermined number of patients have been treated and evaluated, as per predefined stopping rules.

6.9.3 Sample Size Determination  
The sample size of 100 patients is based on assumptions about the expected ORR and the precision of the estimate required. Power calculations were performed to ensure a high probability (power) of detecting a clinically meaningful difference from historical control rates, assuming a two-sided alpha level.

6.9.4 Handling of Missing Data  
Missing data will be handled using appropriate imputation methods or sensitivity analyses to assess the impact of missing data on study conclusions. The reasons for missing data will be investigated and reported.

6.9.5 Statistical Software  
All statistical analyses will be performed using the latest version of a recognized statistical software package, such as SAS or R.

6.9.6 Significance Level  
The significance level for the primary endpoint will be set at an alpha of 0.05, two-sided. Adjustments for multiple testing will be applied if necessary.

6.9.7 Data Monitoring Committee  
An independent data monitoring committee (DMC) may be established to periodically review accumulating data to ensure the safety of participants and the validity and integrity of the data.

6.9.8 Final Analysis  
The final analysis will occur after all patients have completed the study or have discontinued early. The analysis will follow the pre-specified statistical analysis plan, and results will be reported according to CONSORT guidelines or other relevant reporting standards.

# 8. Safety

7. SAFETY

7.1 Safety Monitoring

All patients will be closely monitored for safety throughout the study. Safety assessments will include monitoring and recording all adverse events (AEs), serious adverse events (SAEs), and changes in laboratory values, vital signs, and physical examination findings. Adverse events will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

7.2 Reporting of Adverse Events

Adverse events will be reported by the study staff as they occur. All AEs and SAEs will be documented in the patient's case report form (CRF) with information on the onset, duration, severity, relationship to the study drug, action taken, and outcome.

7.3 Management of Adverse Events

The management of AEs will be at the discretion of the investigator, who will provide appropriate medical care and determine any necessary adjustments to the study treatment, including dose modifications, treatment delays, or discontinuation of the study drug.

7.4 Dose Modifications for Toxicity

Dose modifications for toxicity will be based on the severity and type of AE experienced by the patient. The protocol includes predefined criteria for dose reductions, treatment holds, and discontinuation related to specific AEs.

7.5 Serious Adverse Event Reporting

All SAEs must be reported to the sponsor and the regulatory authorities within 24 hours of the study staff becoming aware of the event. Follow-up information on SAEs must be provided until resolution or stabilization.

7.6 Data Safety Monitoring Board (DSMB)

A DSMB may be established to periodically review safety data and provide independent oversight to ensure the safety of participants. The DSMB will have the authority to recommend modifications to the study or to stop the study if safety concerns arise.

7.7 Safety Endpoints

The safety endpoints of the study include the incidence, nature, and severity of AEs and SAEs, changes in laboratory values, vital signs, and physical examination findings. These will be summarized using descriptive statistics.

7.8 Early Termination Due to Safety Concerns

The study may be terminated early if there is evidence of unexpected, severe toxicity that is related to the study drug, or if there are changes in the risk-benefit ratio that warrant termination.

7.9 Patient Withdrawal Due to Adverse Events

Patients have the right to withdraw from the study at any time. In addition, patients may be withdrawn from the study treatment due to AEs as per the predefined criteria in the protocol.

7.10 Post-Study Follow-Up

Patients will be followed for a specified period after the end of treatment to monitor for late-emerging AEs and to ensure proper management of any ongoing toxicities.

7.11 Training and Education

All study personnel will be trained on the protocol's safety procedures, including the recognition, management, and reporting of AEs and SAEs.

7.12 Safety Analysis

The safety analysis will be performed on the safety population, which includes all patients who received at least one dose of amivantamab. Safety data will be presented by the number and percentage of patients experiencing each AE and will be stratified by severity and relationship to the study drug.

7.13 Communication of Safety Information

All relevant safety information will be communicated to the investigators, the IRB/ethics committee, and regulatory authorities in accordance with local regulations and the study's safety reporting procedures.