Clinical Trial Protocol

# 1. Title

Title

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

Background & Rationale

Colorectal cancer represents a significant public health challenge as a leading cause of cancer-related deaths worldwide. For patients with advanced-stage disease, therapeutic options are limited, particularly for those whose tumors harbor alterations in the epidermal growth factor receptor (EGFR) and the mesenchymal-epithelial transition (MET) pathways. Amivantamab, a novel bispecific antibody that simultaneously targets both EGFR and MET, has shown promising results in non-small cell lung cancer (NSCLC). Given the similarities in EGFR and MET pathway alterations in NSCLC and colorectal cancer, there is a strong rationale to investigate the efficacy and safety of amivantamab in the treatment of advanced colorectal cancer.

Study Objectives

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

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

Study Design

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

Key Inclusion Criteria  
• Adult patients (≥18 years of age) diagnosed with advanced or metastatic colorectal cancer.  
• Genetic confirmation of EGFR and MET pathway alterations in tumor tissue.  
• Disease progression following standard therapy, or for whom no standard treatment options are available.

Treatment Plan

Eligible patients will receive amivantamab administered intravenously at the recommended Phase 2 dose on the first day of each 21-day cycle. Dosage adjustments will be made as necessary based on individual patient tolerance and side effect profile.

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) as per CTCAE v5.0.

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 analyses will focus on survival endpoints, including PFS and OS.

Timeline

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

# 2. Background

Background & Rationale

Colorectal Cancer: A Public Health Challenge  
Colorectal cancer is a major cause of morbidity and mortality worldwide, ranking as one of the leading causes of cancer-related deaths. The disease often progresses to an advanced stage by the time of diagnosis, at which point treatment options become more limited and less effective. The prognosis for patients with advanced colorectal cancer remains poor, highlighting the urgent need for novel therapeutic strategies.

EGFR and MET Pathway Alterations in Colorectal Cancer  
Alterations in the epidermal growth factor receptor (EGFR) and the mesenchymal-epithelial transition (MET) pathways are known to play a critical role in the pathogenesis and progression of several cancers, including colorectal cancer. These alterations can lead to uncontrolled cell growth, evasion of apoptosis, and increased metastatic potential. Current treatments targeting these pathways have shown benefit, but their efficacy is often limited by the development of resistance or the presence of concurrent alterations in both pathways.

Amivantamab: A Bispecific Antibody Approach  
Amivantamab is an innovative bispecific antibody designed to simultaneously target both EGFR and MET receptors. This dual targeting has the potential to overcome resistance mechanisms and provide a more effective treatment option for patients with alterations in these pathways. Amivantamab has already demonstrated efficacy in non-small cell lung cancer (NSCLC), a cancer type that shares molecular similarities with colorectal cancer in terms of EGFR and MET alterations.

Rationale for Study in Colorectal Cancer  
Given the success of amivantamab in NSCLC and the overlap in molecular alterations with colorectal cancer, there is a compelling rationale to extend the investigation of amivantamab to patients with advanced colorectal cancer. This Phase 2 study is designed to evaluate the safety and efficacy of amivantamab in this new patient population, with the hope of providing a much-needed treatment option for those with limited therapeutic alternatives.

Study Objectives

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

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

Study Design

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

Key Inclusion Criteria  
• Adult patients (≥18 years of age) diagnosed with advanced or metastatic colorectal cancer.  
• Genetic confirmation of EGFR and MET pathway alterations in tumor tissue.  
• Disease progression following standard therapy, or for whom no standard treatment options are available.

Treatment Plan

Eligible patients will receive amivantamab administered intravenously at the recommended Phase 2 dose on the first day of each 21-day cycle. Dosage adjustments will be made as necessary based on individual patient tolerance and side effect profile.

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) as per CTCAE v5.0.

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 analyses will focus on survival endpoints, including PFS and OS.

Timeline

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

# 3. Objectives

Objectives

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

Secondary Objectives  
• To evaluate the progression-free survival (PFS) of patients treated with amivantamab.  
• To assess the overall survival (OS) of the study cohort.  
• To determine the disease control rate (DCR) in the treated population.  
• To characterize the safety and tolerability 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 evaluate the efficacy and safety of amivantamab in patients with advanced colorectal cancer who have documented alterations in the epidermal growth factor receptor (EGFR) and the mesenchymal-epithelial transition (MET) pathways.

Study Population

The study will enroll approximately 100 adult patients (≥18 years of age) diagnosed with advanced or metastatic colorectal cancer. Eligibility for participation includes genetic confirmation of EGFR and MET pathway alterations in tumor tissue and disease progression following standard therapy, or for patients for whom no standard treatment options are available.

Intervention

Participants will receive amivantamab administered intravenously at the recommended Phase 2 dose on the first day of each 21-day cycle. Dosage adjustments will be made as necessary based on individual patient tolerance and side effect profile.

Duration

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

Treatment Administration and Monitoring

Treatment will be administered on an outpatient basis. Patients will be closely monitored throughout the study for signs of toxicity, adverse events, and response to therapy. Dose modifications, interruptions, or discontinuation will be guided by predefined safety criteria.

Study Assessments

Efficacy assessments will be conducted using RECIST v1.1 criteria to evaluate the primary endpoint of objective response rate (ORR). Secondary endpoints, including progression-free survival (PFS), overall survival (OS), and disease control rate (DCR), will be assessed at regular intervals. Safety will be monitored continuously, with adverse events graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Follow-Up

After the completion of treatment, patients will enter a follow-up phase for the assessment of long-term outcomes and late-emerging toxicities. The follow-up visits will include clinical assessments, imaging studies, and laboratory tests as per the study protocol.

Data Collection and Management

Data will be collected systematically using electronic case report forms (eCRFs). The data management team will ensure the accuracy and completeness of the data. All study-related information will be stored securely and will be accessible only to authorized personnel.

Ethics and Regulatory Compliance

The study will be conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines, and all applicable regulatory requirements. The protocol, informed consent forms, and any other relevant study documentation will be reviewed and approved by an Institutional Review Board (IRB) or Ethics Committee (EC) before the study commences.

Study Completion

The study will be considered complete after the last patient's last visit or after the final data analysis, whichever occurs later. Results will be disseminated through scientific publications and presentations at medical conferences.

# 5. Population

Population

Study Population

The study will include a total of 100 adult patients (≥18 years of age) diagnosed with advanced or metastatic colorectal cancer. The population will be characterized by the following inclusion criteria:

Inclusion Criteria  
• Adult patients aged 18 years or older.  
• Histologically or cytologically confirmed diagnosis of advanced or metastatic colorectal cancer.  
• Documented alterations in the EGFR and MET pathways within the tumor tissue, as confirmed by a validated molecular assay.  
• Disease progression on or following the most recent standard therapy, or for patients for whom no standard treatment options are available, as determined by the treating physician.  
• Measurable disease as defined by RECIST v1.1 criteria.  
• An Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.  
• Adequate organ function as defined by study-specific laboratory criteria.  
• Ability to understand and willingness to sign a written informed consent document.

Exclusion Criteria  
• Prior treatment with any drug specifically targeting EGFR and MET pathways for their colorectal cancer.  
• Known symptomatic brain metastases requiring steroids.  
• 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.  
• Pregnant or breastfeeding women, due to the potential for congenital abnormalities and the potential of this regimen to harm nursing infants.  
• Known hypersensitivity to any component of amivantamab or its excipients.

Screening and Enrollment

Patients will be screened for eligibility based on medical history, physical examination, laboratory tests, and tumor molecular profiling. Upon confirmation of eligibility, patients will be enrolled in the study and will commence treatment with amivantamab as per the treatment plan.

Withdrawal Criteria

Participants may withdraw from the study at any time for any reason. Additionally, the study investigators may discontinue a participant from the study for the following reasons:  
• Intolerable adverse events.  
• Non-compliance with study protocol or procedures.  
• Disease progression as defined by RECIST v1.1 criteria.  
• Any change in the patient's condition that, in the opinion of the investigator, precludes further study participation.

Replacement of Participants

Participants who withdraw from the study will not be replaced. The study aims to enroll approximately 100 patients to ensure adequate power for statistical analyses, accounting for potential dropouts.

Ethical Considerations

The study protocol and all related documents will be reviewed and approved by an Institutional Review Board (IRB) or Ethics Committee (EC) prior to patient enrollment. Informed consent will be obtained from all participants before any study-related procedures are conducted. Patient confidentiality will be maintained throughout the study in accordance with HIPAA regulations and applicable laws.

# 6. Procedures

Procedures

Screening and Baseline Assessments

Informed Consent  
• Obtain written informed consent from each potential participant before conducting any study-related procedures.

Eligibility Confirmation  
• Review medical history and perform a physical examination.  
• Conduct laboratory tests to ensure adequate organ function.  
• Perform tumor molecular profiling to confirm EGFR and MET pathway alterations.  
• Verify measurable disease according to RECIST v1.1 criteria.  
• Assess ECOG performance status.

Enrollment  
• Enroll eligible patients and assign a unique patient identification number.

Treatment Administration

Initial Dosing  
• Administer intravenous amivantamab at the recommended Phase 2 dose on Day 1 of each 21-day cycle.

Dose Adjustments  
• Adjust the dose of amivantamab based on individual patient tolerance and side effect profile, following predefined criteria.

Treatment Monitoring  
• Monitor patients for signs of toxicity and adverse events throughout the treatment period.  
• Record all adverse events and grade them according to CTCAE v5.0.

Efficacy and Safety Assessments

Efficacy Evaluations  
• Conduct imaging studies as per RECIST v1.1 to assess ORR, PFS, OS, and DCR at specified intervals.

Safety Evaluations  
• Monitor and record all adverse events throughout the study.  
• Perform laboratory tests to monitor organ function and detect potential treatment-related toxicities.

Follow-Up Phase

Post-Treatment Follow-Up  
• After treatment completion, schedule follow-up visits for long-term outcome assessments and monitoring of late-emerging toxicities.  
• Continue imaging studies and laboratory tests as per the study protocol.

Data Collection and Management

Data Recording  
• Utilize electronic case report forms (eCRFs) for systematic data collection.  
• Ensure accuracy and completeness of data by the data management team.

Data Storage and Access  
• Store all study-related information securely.  
• Allow access to data only to authorized study personnel.

Study Completion

Final Assessments  
• Conduct final assessments as per protocol after the last patient's last visit or upon final data analysis, whichever is later.

Data Analysis and Dissemination  
• Analyze collected data to evaluate study endpoints.  
• Prepare and disseminate study results through scientific publications and conference presentations.

Ethical and Regulatory Compliance

IRB/EC Review  
• Ensure that the study protocol, informed consent forms, and other relevant documents have been reviewed and approved by an Institutional Review Board (IRB) or Ethics Committee (EC) before the study commences.

Compliance with Guidelines  
• Conduct the study in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines, and all applicable regulatory requirements.

Participant Withdrawal and Discontinuation

Withdrawal by Participant  
• Allow participants to withdraw from the study at any time for any reason.

Discontinuation by Investigator  
• Discontinue participants from the study for intolerable adverse events, non-compliance, disease progression, or any condition that precludes further participation as judged by the investigator.

Replacement of Participants  
• Do not replace participants who withdraw from the study. The sample size accounts for potential dropouts to ensure statistical power.

# 7. Statistical Analysis

Statistical Analysis

Overview

The statistical analysis plan for this Phase 2 study of amivantamab in patients with advanced colorectal cancer will outline the methods for evaluating the primary and secondary endpoints, handling of missing data, and the statistical tests to be used.

Sample Size Determination

The sample size of 100 patients was determined to provide adequate power to detect a clinically meaningful difference in the primary endpoint of objective response rate (ORR). The power calculation assumes a two-sided alpha level of 0.05 and is based on historical control data of ORR in similar patient populations.

Analysis Populations  
• Intent-to-Treat (ITT) Population: All enrolled patients who receive at least one dose of amivantamab will be included in the ITT population for efficacy analyses.  
• Safety Population: All patients who receive at least one dose of amivantamab and have at least one post-baseline safety assessment will be included in the safety analyses.

Primary Endpoint Analysis  
• Objective Response Rate (ORR): The ORR, defined as the proportion of patients with a partial or complete response to therapy, will be calculated along with a two-sided 95% confidence interval using the Clopper-Pearson method.

Secondary Endpoint Analyses  
• Progression-Free Survival (PFS): PFS will be analyzed using the Kaplan-Meier method, and median PFS will be estimated with a 95% confidence interval. The log-rank test will be used to compare PFS across predefined subgroups.  
• Overall Survival (OS): OS will also be analyzed using the Kaplan-Meier method, with median OS estimated and compared across subgroups using the log-rank test.  
• Disease Control Rate (DCR): DCR will be calculated as the proportion of patients with complete response, partial response, or stable disease, with a 95% confidence interval using the Clopper-Pearson method.  
• Safety Profile: Adverse events will be summarized using frequencies and percentages. The severity of adverse events will be graded according to CTCAE v5.0.

Interim Analyses

No interim efficacy analyses are planned for this study. However, safety data will be reviewed periodically by an independent data monitoring committee to ensure patient safety.

Handling of Missing Data

Missing data will be handled using the last observation carried forward (LOCF) approach for efficacy endpoints. For safety data, patients will be analyzed according to the actual treatment received, and missing data will not be imputed.

Statistical Software

All statistical analyses will be performed using SAS software (SAS Institute Inc., Cary, NC, USA) or an equivalent statistical package.

Significance Levels

All tests will be two-sided, with a significance level set at 0.05. No adjustments for multiple comparisons will be made.

Subgroup Analyses

Exploratory subgroup analyses may be conducted based on demographic and baseline characteristics to investigate potential heterogeneity of treatment effects.

Final Analysis

The final analysis will be conducted after all patients have completed the study or have discontinued early. The primary and secondary endpoints will be analyzed as per the statistical methods outlined above.

Reporting of Results

Results will be reported in accordance with the CONSORT guidelines for clinical trials. Summary tables, figures, and listings will be generated to provide a comprehensive overview of the study outcomes.

# 8. Safety

Safety

Safety Monitoring

Safety monitoring will be a continuous process throughout the study, with adverse events (AEs) recorded and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The study will implement a robust safety monitoring plan that includes:  
• Regular assessment of vital signs, physical examinations, and laboratory tests to monitor organ function and detect potential treatment-related toxicities.  
• Immediate reporting and management of AEs, serious adverse events (SAEs), and suspected unexpected serious adverse reactions (SUSARs).  
• Periodic safety reviews by an independent data monitoring committee to ensure ongoing patient safety.

Adverse Event Management

Participants will be educated on the potential side effects of amivantamab and instructed to report any symptoms promptly. The study staff will be trained to recognize and manage AEs effectively. Management may include:  
• Dose adjustments, interruptions, or discontinuation of amivantamab based on predefined safety criteria.  
• Supportive care measures to alleviate symptoms.  
• Referral to a specialist if required for the management of complex AEs.

Reporting of Adverse Events

All AEs will be documented in the patient's medical record and in the electronic case report form (eCRF). The severity of AEs will be graded, and the relationship to the study drug will be assessed by the investigator. Reporting will follow regulatory requirements and the study's standard operating procedures, which include timelines for reporting SAEs and SUSARs to regulatory authorities and the IRB/EC.

Safety Endpoints

The safety endpoints of the study will include:  
• Incidence and severity of AEs and SAEs.  
• Changes in laboratory parameters indicative of organ function.  
• Proportion of patients requiring dose modifications due to AEs.  
• Proportion of patients discontinuing treatment due to AEs.

Data Safety Monitoring Board (DSMB)

An independent DSMB will be established to periodically review accumulated safety data and provide recommendations on the continuation, modification, or termination of the study based on safety concerns.

Patient Withdrawal due to Adverse Events

Patients have the right to withdraw from the study at any time. Additionally, the investigator may decide to withdraw a patient from the study due to AEs that are deemed to compromise patient safety or affect the integrity of the study data.

Post-Study Follow-up

Upon completion of the study treatment, patients will enter a follow-up phase to monitor for long-term safety and late-emerging toxicities. This phase will include scheduled visits and assessments as per the study protocol.

Safety Reporting to Regulatory Authorities

All safety data will be summarized and reported to regulatory authorities as required by law and in accordance with the study's safety reporting plan. This will include periodic safety update reports and the final study report.

Ethics and Patient Safety

The study will be conducted in full compliance with the ethical principles of the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines, and all applicable regulatory requirements to ensure the safety and rights of participants are protected.