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 disease is poor, with few effective treatment options available. Alterations in the epidermal growth factor receptor (EGFR) and the mesenchymal-epithelial transition (MET) pathways are implicated in the pathogenesis and progression of colorectal cancer. Amivantamab is a novel bispecific antibody that simultaneously targets EGFR and MET and has shown promise in treating non-small cell lung cancer (NSCLC). This Phase 2 study will investigate the safety and efficacy of amivantamab in patients with advanced colorectal cancer who have EGFR and MET alterations.

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

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 pathway alterations.

Key Inclusion Criteria  
• Adult patients (≥18 years of age) diagnosed with advanced or metastatic colorectal cancer.  
• Presence of EGFR and MET pathway alterations confirmed by molecular testing.  
• Disease progression following standard therapy, or those who are ineligible for existing standard treatment options.

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 and response.

Study Endpoints

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

Secondary Endpoints  
• Progression-free survival (PFS) as measured from the start of treatment to the time of progression or death from any cause.  
• Overall survival (OS) as measured from the start of treatment to the time of death from any cause.  
• Disease control rate (DCR) as a composite of complete response, partial response, and stable disease.  
• Incidence and severity of adverse events as classified by 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 endpoints will be analyzed to provide additional efficacy and safety data.

Timeline

The estimated duration of the study is 24 months, which includes patient enrollment, treatment, follow-up, and 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 worldwide. The prognosis for patients diagnosed with advanced-stage CRC is particularly grim, with median survival times that highlight the urgent need for more effective therapeutic options. Standard treatments, including chemotherapy and targeted therapies, often provide limited benefits and are associated with considerable toxicity.

Recent advances in molecular biology have identified key genetic alterations that drive CRC pathogenesis, among which are mutations and amplifications in the epidermal growth factor receptor (EGFR) and the mesenchymal-epithelial transition (MET) pathways. These alterations not only contribute to tumor growth and metastasis but also to resistance mechanisms against existing therapies.

Amivantamab is a bispecific antibody designed to target both EGFR and MET receptors simultaneously, thereby potentially overcoming resistance mechanisms and providing a new therapeutic strategy for patients with CRC harboring these alterations. In non-small cell lung cancer (NSCLC), amivantamab has demonstrated promising efficacy and an acceptable safety profile, suggesting its potential utility in other EGFR and MET-driven cancers.

Given the unmet medical need and the preliminary evidence of amivantamab's activity in NSCLC, this Phase 2 study aims to explore the therapeutic value of amivantamab in the advanced CRC patient population with documented EGFR and MET alterations. The study will provide critical data on the safety and efficacy of amivantamab, potentially offering a novel treatment avenue for these patients.

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# 4. Study Design

Study Design

Overview  
This clinical investigation 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 exhibit alterations in the EGFR and MET pathways.

Study Population  
The study will enroll approximately 100 adult patients (≥18 years of age) diagnosed with advanced or metastatic colorectal cancer. All participants must have documented EGFR and MET pathway alterations and must have experienced disease progression following standard therapy or be ineligible for existing 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 individual patient tolerance and response to treatment.

Duration  
The treatment will continue until disease progression, unacceptable toxicity, withdrawal of consent, or other criteria for discontinuation are met. The estimated study duration is 24 months, encompassing patient enrollment, treatment, follow-up, and final data analysis.

Follow-Up  
Patients will be monitored for response to treatment, progression of disease, overall survival, and any adverse events. Follow-up assessments will be conducted in accordance with the study protocol to evaluate the long-term safety and efficacy of amivantamab.

Study Endpoints  
The primary endpoint of the study is the objective response rate (ORR), as measured by RECIST v1.1 criteria. Secondary endpoints include progression-free survival (PFS), overall survival (OS), disease control rate (DCR), and the incidence and severity of adverse events as classified by CTCAE v5.0.

Statistical Analysis  
The sample size of 100 patients is calculated to provide adequate power to detect a clinically meaningful difference in the primary endpoint of ORR. Secondary analyses will be conducted for PFS, OS, DCR, and safety data to provide a comprehensive understanding of the treatment's impact.

Ethics and Regulatory Compliance  
The study will be conducted in accordance with Good Clinical Practice (GCP) guidelines, ethical principles that have their origin in the Declaration of Helsinki, and applicable regulatory requirements. An independent ethics committee or institutional review board will approve the study protocol prior to initiation.

Data Monitoring  
A Data Monitoring Committee (DMC) will be established to periodically review and evaluate the accumulated study data for participant safety, study conduct, and progress, and, if necessary, recommend modifications to the study.

Study Completion  
The study is considered complete after the last patient's last visit or the last required data collection for endpoint analysis, whichever occurs later. The final analysis will be conducted after all patients have completed the study or have discontinued early.

# 5. Population

5. STUDY POPULATION

5.1 Inclusion Criteria  
To be eligible for participation in this Phase 2 study, patients must meet the following criteria:

1. Age and Disease State:  
• Adult patients (≥18 years of age).  
• Diagnosed with advanced or metastatic colorectal cancer.

2. Genetic Alterations:  
• Documented alterations in the EGFR and MET pathways, confirmed by molecular testing.

3. Treatment History:  
• Patients must have experienced disease progression following standard therapy.  
• Patients who are ineligible for existing standard treatment options due to contraindications or other reasons.

4. Other Considerations:  
• Ability to understand and willingness to sign a written informed consent form.  
• Adequate organ function as defined by study-specific laboratory tests.  
• Performance status score indicating the patient is capable of receiving treatment.

5.2 Exclusion Criteria  
Patients will be excluded from the study if they meet any of the following criteria:

1. Prior Therapies:  
• Treatment with any other investigational agent within 28 days prior to enrollment.  
• Prior therapy specifically targeting EGFR and MET pathways within a specified timeframe before the first dose of amivantamab.

2. Medical Conditions:  
• Known brain metastases that are untreated, symptomatic, or require therapy to control symptoms.  
• Significant cardiovascular disease, such as uncontrolled arrhythmia or uncontrolled hypertension.  
• Active infection or other medical conditions that could interfere with the patient's participation in the study.

3. Other Treatments:  
• Concurrent chemotherapy, immunotherapy, or radiotherapy during the study period.  
• Use of other targeted therapy or biologic agents that could interfere with the study outcomes.

4. Pregnancy:  
• Pregnant or breastfeeding women.  
• Women of childbearing potential not using effective contraception.

5. Allergies:  
• Known hypersensitivity to amivantamab or its excipients.

5.3 Withdrawal Criteria  
Participants may withdraw from the study at any time for any reason. Additionally, the study investigators may withdraw participants from the study for the following reasons:

1. Safety:  
• Occurrence of intolerable adverse events.  
• Significant changes in the participant's health status that make continued participation unsafe.

2. Non-Compliance:  
• Non-adherence to study protocol or treatment regimen.  
• Missed visits or failure to complete required tests that impact the integrity of the study data.

3. Study Specifics:  
• Lack of therapeutic effect as determined by predefined study endpoints.  
• Patient's decision to withdraw consent for continued participation.

Participants who withdraw from the study will undergo an end-of-study evaluation and will be followed up as per the study protocol to capture any adverse events and to ensure their safety.

# 6. Procedures

6. PROCEDURES

6.1 Screening and Enrollment

6.1.1 Initial Evaluation  
• Obtain written informed consent from participants.  
• Review medical history and prior treatments.  
• Perform physical examination and assessment of performance status.  
• Conduct laboratory tests to confirm adequate organ function.  
• Verify EGFR and MET pathway alterations through molecular testing.  
• Assess eligibility based on inclusion and exclusion criteria.

6.1.2 Enrollment  
• Register eligible participants into the study.  
• Assign unique participant identification numbers.

6.2 Treatment Administration

6.2.1 Dosage and Administration  
• Administer intravenous amivantamab at the recommended Phase 2 dose on Day 1 of each 21-day cycle.  
• Monitor patients for infusion-related reactions and manage according to protocol.

6.2.2 Dose Adjustments  
• Adjust doses based on individual patient tolerance and response, following predefined criteria.  
• Delay or modify doses in the event of adverse reactions as per protocol guidelines.

6.3 Monitoring and Assessments

6.3.1 Efficacy Assessments  
• Measure tumor response using RECIST v1.1 criteria at specified intervals.  
• Record progression-free survival (PFS) and overall survival (OS) data.  
• Calculate disease control rate (DCR) as a composite of complete response, partial response, and stable disease.

6.3.2 Safety Assessments  
• Monitor and record adverse events using CTCAE v5.0.  
• Perform routine laboratory tests to monitor organ function and detect potential toxicities.  
• Document any serious adverse events and take appropriate action as per safety protocols.

6.4 Follow-Up

6.4.1 During Treatment  
• Conduct regular follow-up visits to assess treatment response and manage side effects.  
• Update consent and data privacy forms as necessary.

6.4.2 Post-Treatment  
• Schedule follow-up visits after treatment discontinuation to monitor long-term effects and disease status.  
• Collect final data for endpoint analysis.

6.5 Discontinuation of Treatment

6.5.1 Criteria for Discontinuation  
• Disease progression as defined by RECIST v1.1.  
• Unacceptable toxicity despite dose adjustments.  
• Withdrawal of consent by the participant.  
• Any significant change in the participant's health status warranting cessation of treatment.

6.5.2 Procedures for Discontinuation  
• Perform an end-of-treatment evaluation, including physical examination and laboratory tests.  
• Provide appropriate post-study care referrals as needed.  
• Continue to follow up for adverse events and survival status per protocol.

6.6 Data Collection and Management

6.6.1 Data Recording  
• Record all data in case report forms (CRFs) or electronic data capture (EDC) systems.  
• Ensure accuracy and completeness of data entry.

6.6.2 Data Review and Quality Control  
• Conduct regular data monitoring to ensure data quality and protocol compliance.  
• Implement data verification procedures to validate the collected data.

6.7 Study Completion

6.7.1 Final Assessments  
• Conduct final assessments for all participants, including those who discontinued early.  
• Collect and review all data required for endpoint analysis.

6.7.2 Data Analysis and Reporting  
• Analyze data according to the statistical analysis plan.  
• Prepare study reports and disseminate findings through publications and presentations.

6.8 Ethical Considerations  
• Ensure ongoing compliance with ethical guidelines and regulatory requirements.  
• Report any protocol amendments to the ethics committee or institutional review board.  
• Maintain participant confidentiality and data privacy throughout the study.

# 7. Statistical Analysis

7. STATISTICAL ANALYSIS

7.1 General Considerations

Statistical analyses will be performed using a pre-specified statistical analysis plan (SAP), which will be finalized prior to database lock. The level of significance will be set at 0.05, and all tests will be two-sided unless otherwise specified. The primary analysis will be based on the intention-to-treat (ITT) population, which includes all patients who received at least one dose of amivantamab. Per protocol and as-treated analyses may also be conducted as sensitivity analyses.

7.2 Sample Size Determination

The sample size of 100 patients is estimated to provide sufficient power to detect a clinically meaningful improvement in the primary endpoint of objective response rate (ORR). The power calculation assumes a baseline ORR from historical controls and an expected increase in ORR with amivantamab treatment. The exact figures used for power calculations will be detailed in the SAP.

7.3 Analysis of Primary Endpoint

The primary endpoint, 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 95% confidence interval (CI) for the ORR will be estimated using the Clopper-Pearson method.

7.4 Analysis of Secondary Endpoints

Secondary endpoints, including progression-free survival (PFS), overall survival (OS), and disease control rate (DCR), will be analyzed using appropriate statistical methods:  
• PFS and OS will be estimated using the Kaplan-Meier method, and median times with 95% CIs will be reported.  
• DCR will be calculated as the proportion of patients who achieve a CR, PR, or stable disease (SD), with 95% CI estimated similarly to ORR.  
• Safety data will be summarized using descriptive statistics. Adverse events will be tabulated and graded according to CTCAE v5.0.

7.5 Interim Analysis

An interim analysis may be planned to assess safety, futility, or efficacy, as determined by the Data Monitoring Committee (DMC). The timing and stopping rules for interim analysis will be specified in the SAP.

7.6 Handling of Missing Data

The approach to handling missing data will be outlined in the SAP. This may include methods such as last observation carried forward (LOCF) or multiple imputation, depending on the nature and extent of the missing data.

7.7 Subgroup Analyses

Subgroup analyses may be conducted to explore the consistency of treatment effects across various patient subgroups, such as age, sex, baseline performance status, and molecular characteristics of EGFR and MET alterations. These analyses will be exploratory in nature and will be interpreted with caution.

7.8 Statistical Software

All statistical analyses will be performed using validated statistical software. The specific software and version will be documented in the SAP.

7.9 Reporting of Results

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 comprehensive details of the statistical methods and findings.

# 8. Safety

8. SAFETY

8.1 Safety Monitoring

Participants will be closely monitored for safety throughout the study. Safety assessments will include physical examinations, vital sign measurements, laboratory tests, and the monitoring of adverse events (AEs). All AEs will be recorded and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

8.2 Reporting of Adverse Events

All AEs, regardless of severity or relation to the study drug, must be reported to the study investigators. Serious adverse events (SAEs) must be reported within 24 hours of the investigator becoming aware of the event. The study team will follow up on all AEs until resolution or stabilization, or until it is determined that the study treatment is not the cause.

8.3 Management of Adverse Events

The study protocol includes detailed guidelines for the management of specific AEs associated with amivantamab. Dose adjustments, including dose interruptions or reductions, will be made in accordance with these guidelines to manage toxicity. If necessary, treatment may be discontinued due to intolerable toxicity.

8.4 Infusion-Related Reactions

Given that amivantamab is administered intravenously, there is a potential for infusion-related reactions. Patients will be premedicated as per protocol to minimize the risk of these reactions. Any infusion-related reactions will be managed according to the protocol, which may include slowing or stopping the infusion, providing symptomatic treatment, and adjusting future dosing schedules.

8.5 Data Monitoring Committee (DMC)

A DMC will be established to periodically review safety data and other study parameters. The DMC will have the authority to recommend modifications to the study or to halt the study if safety concerns arise.

8.6 Safety Endpoints

The safety endpoints of the study include the incidence, nature, and severity of AEs and SAEs. Additional safety endpoints include changes in laboratory values, vital signs, and any other clinically significant changes in health status.

8.7 Early Termination Due to Safety Issues

Participants may be withdrawn from the study treatment if they experience AEs that meet the criteria for discontinuation as per the study protocol. The criteria for early termination due to safety concerns will be clearly defined and may include factors such as specific toxicities, allergic reactions, or any other safety risks identified during the study.

8.8 Post-Study Follow-Up

After discontinuation of the study drug, patients will be followed up for a specified period to monitor for any late-emerging AEs or other safety issues. The follow-up schedule will be outlined in the study protocol.

8.9 Safety Reporting to Regulatory Authorities

All SAEs and other significant safety findings will be reported to regulatory authorities in accordance with local laws and regulations. This will ensure that safety concerns are communicated promptly and appropriately managed.

8.10 Patient Education and Informed Consent

Participants will be informed of the potential risks and AEs associated with amivantamab during the informed consent process. They will be provided with information on how to recognize potential AEs and instructed on when and how to report them to the study team.

8.11 Safety Review and Risk Mitigation

The study protocol includes a risk mitigation plan to address known and potential safety risks associated with amivantamab. This plan will be reviewed and updated as necessary based on emerging safety data during the study.

8.12 Ethics and Participant Welfare

The study will be conducted in accordance with ethical principles and with respect for the rights, safety, and well-being of the participants. The study protocol, including the safety monitoring plan, will be approved by an independent ethics committee or institutional review board before the study commences.