Clinical Trial Protocol

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1. Protocol Title

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, with limited effective treatments for advanced-stage patients, particularly those with EGFR and MET pathway alterations. Amivantamab, a bispecific antibody targeting EGFR and MET, has demonstrated efficacy in non-small cell lung cancer (NSCLC). This Phase 2 study aims to evaluate its safety and effectiveness in advanced colorectal cancer patients.  
Study Objectives  
Primary Objective  
• To assess the objective response rate (ORR) of amivantamab in patients with EGFR and MET alterations.  
Secondary Objectives  
• To evaluate progression-free survival (PFS), overall survival (OS), disease control rate (DCR), and safety profile.  
Study Design  
Single-arm, open-label, Phase 2 study of amivantamab in patients with advanced colorectal cancer.  
Key Inclusion Criteria  
• Adults aged 18 or older with advanced or metastatic colorectal cancer.  
• Documented EGFR and MET pathway alterations.  
• Progression on or after standard therapy, or patients with no available standard treatment options.  
Treatment Plan  
Patients will receive intravenous amivantamab at the recommended Phase 2 dose on Day 1 of each 21-day cycle, with adjustments based on patient tolerance.  
Study Endpoints  
Primary Endpoint  
• Objective response rate (ORR).  
Secondary Endpoints  
• Progression-free survival (PFS), overall survival (OS), disease control rate (DCR), and adverse events.  
Statistical Considerations  
A sample size of 100 patients will provide adequate power to detect a clinically meaningful ORR, with secondary analyses for survival endpoints.  
Timeline  
Estimated study duration is 24 months from enrollment to final data analysis.

2. Background

Background & Rationale  
Epidemiology of Colorectal Cancer  
Colorectal cancer (CRC) is one of the most common malignancies worldwide and a leading cause of cancer-related deaths. The incidence and mortality rates vary globally, with higher prevalence in developed countries. Despite advancements in screening and treatment, the prognosis for patients with advanced-stage CRC remains poor.  
Current Treatment Landscape  
The standard treatment for advanced CRC typically involves a combination of surgery, chemotherapy, and radiation therapy. Targeted therapies have also been incorporated into treatment regimens, particularly for patients with specific genetic profiles. However, the effectiveness of these treatments is often limited by the development of resistance and disease progression.  
EGFR and MET Pathway Alterations in CRC  
Alterations in the epidermal growth factor receptor (EGFR) and the mesenchymal-epithelial transition (MET) pathway have been identified in a subset of CRC patients. These alterations are associated with aggressive tumor behavior and poor prognosis. Current EGFR-targeted therapies have shown limited success, and there is a need for novel therapeutic strategies to address these alterations.  
Rationale for Amivantamab in CRC  
Amivantamab is a bispecific antibody that simultaneously targets EGFR and MET, potentially overcoming resistance mechanisms and providing a new therapeutic option for patients with alterations in these pathways. Its efficacy has been previously demonstrated in non-small cell lung cancer (NSCLC), suggesting a potential benefit in CRC.  
Justification for Phase 2 Study  
Given the unmet medical need for effective treatments in advanced CRC with EGFR and MET alterations, and the promising results from NSCLC studies, a Phase 2 study of amivantamab is warranted. This study will evaluate the safety and efficacy of amivantamab in this specific patient population, with the potential to improve outcomes and expand the therapeutic arsenal against advanced CRC.  
Study Objectives  
Primary Objective  
• To assess the objective response rate (ORR) of amivantamab in patients with EGFR and MET alterations.  
Secondary Objectives  
• To evaluate progression-free survival (PFS), overall survival (OS), disease control rate (DCR), and safety profile.  
Study Design  
Overview  
This is a single-arm, open-label, Phase 2 study of amivantamab in patients with advanced colorectal cancer.  
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Patients will receive intravenous amivantamab at the recommended Phase 2 dose on Day 1 of each 21-day cycle, with adjustments based on patient tolerance.  
Study Endpoints  
• Primary Endpoint: Objective response rate (ORR).  
• Secondary Endpoints: Progression-free survival (PFS), overall survival (OS), disease control rate (DCR), and adverse events.  
Statistical Considerations  
A sample size of 100 patients will provide adequate power to detect a clinically meaningful ORR, with secondary analyses for survival endpoints.  
Timeline  
Estimated study duration is 24 months from enrollment to final data analysis.

3. Objectives

Study Objectives  
Primary Objective  
• To assess the objective response rate (ORR) of amivantamab in patients with EGFR and MET alterations.  
Secondary Objectives  
• To evaluate progression-free survival (PFS).  
• To evaluate overall survival (OS).  
• To assess the disease control rate (DCR).  
• 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 evaluate the safety and efficacy of amivantamab in patients with advanced colorectal cancer (CRC) harboring epidermal growth factor receptor (EGFR) and MET pathway alterations.  
Study Population  
The study will enroll adults aged 18 years or older diagnosed with advanced or metastatic CRC. All participants must have documented EGFR and MET pathway alterations and must have experienced progression on or after standard therapy, or be patients for whom no standard treatment options are available.  
Intervention  
Participants will receive amivantamab administered intravenously at the recommended Phase 2 dose 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.  
Follow-Up  
Patients will be followed for response to treatment, progression of disease, survival, and long-term adverse events. Follow-up assessments will be conducted according to the schedule of assessments outlined in the protocol.  
Study Endpoints  
Primary Endpoint  
• Objective response rate (ORR), defined as the proportion of patients with a partial or complete response to therapy, as assessed by RECIST v1.1 criteria.  
Secondary Endpoints  
• Progression-free survival (PFS), the time from the start of treatment to disease progression or death from any cause.  
• Overall survival (OS), the time from the start of treatment to death from any cause.  
• Disease control rate (DCR), the proportion of patients who have achieved complete response, partial response, or stable disease.  
• Safety profile, including the incidence and severity of adverse events.  
Statistical Analysis  
The study will include a sample size of 100 patients to provide adequate power to detect a clinically meaningful difference in ORR. Secondary endpoints will be analyzed to provide additional efficacy and safety data.  
Study Timeline  
The estimated duration of the study is 24 months, which includes the time from enrollment of the first participant to the completion of final data analysis.

5. Study Population

Population  
Inclusion Criteria  
• Age and Condition: Participants must be adults aged 18 years or older with a diagnosis of advanced or metastatic colorectal cancer (CRC).  
• Genetic Alterations: All participants must have documented alterations in the epidermal growth factor receptor (EGFR) and MET pathways.  
• Treatment History: Eligible patients must have experienced disease progression on or after standard therapy, or must be individuals for whom no standard treatment options are available.  
Exclusion Criteria  
• Prior Therapy: Patients who have received previous treatment with an EGFR or MET inhibitor may be excluded, depending on the specific criteria outlined in the protocol.  
• Comorbid Conditions: Individuals with significant comorbid conditions that could interfere with the study outcomes or the safety of the intervention may be excluded.  
• Performance Status: Patients with a performance status that indicates poor prognosis or inability to comply with the treatment protocol may be excluded.  
Recruitment and Screening  
• Recruitment Strategy: Patients will be recruited from oncology centers with expertise in managing advanced CRC. Recruitment efforts will include outreach to potential participants through clinician referrals, patient registries, and advocacy groups.  
• Screening Procedures: Potential participants will undergo a screening process that includes a review of their medical history, confirmation of EGFR and MET alterations through genetic testing, and an assessment of their eligibility based on inclusion and exclusion criteria.  
Enrollment  
• Enrollment Target: The study aims to enroll a total of 100 patients to achieve adequate power for detecting a clinically meaningful objective response rate (ORR).  
• Consent Process: Informed consent will be obtained from all participants prior to enrollment in the study. The consent process will involve a detailed explanation of the study's purpose, procedures, potential risks, and benefits.  
Baseline Characteristics  
• Demographics: Baseline demographic data, including age, sex, race, and ethnicity, will be collected for all participants.  
• Disease Characteristics: Information on the stage of cancer, prior treatments, and the presence of EGFR and MET alterations will be documented.  
• Performance Status: Baseline performance status will be assessed using an appropriate scale, such as the Eastern Cooperative Oncology Group (ECOG) performance status.  
Stratification and Randomization  
• Stratification: Given the single-arm nature of the study, there will be no stratification or randomization of participants.  
• Subgroup Analyses: Subgroup analyses may be conducted post hoc to explore the efficacy and safety of amivantamab in various patient subpopulations defined by demographic or disease characteristics.  
Study Withdrawal  
• Discontinuation Criteria: Participants may be withdrawn from the study for reasons including disease progression, unacceptable toxicity, non-compliance with the study protocol, withdrawal of consent, or at the discretion of the investigator.  
• Data Handling: Data from participants who withdraw from the study will be handled according to the pre-specified statistical analysis plan, and efforts will be made to collect follow-up data where possible.

6. Study Procedures

Procedures  
Treatment Administration  
Dosing and Administration  
• Initial Dose: Patients will receive the recommended Phase 2 dose of amivantamab via intravenous infusion.  
• Dosing Schedule: The infusion will be administered on Day 1 of each 21-day cycle.  
• Dose Adjustments: Dose modifications may be necessary based on the patient's tolerance to the treatment. Specific criteria for dose adjustments will be detailed in the protocol.  
Premedication and Supportive Care  
• Premedication: To mitigate infusion-related reactions, premedication guidelines will be followed as per the protocol.  
• Supportive Care: Supportive care measures, including the management of adverse events, will be provided in accordance with standard clinical practices and the study protocol.  
Monitoring and Assessments  
Efficacy Assessments  
• Imaging: Radiographic assessments to evaluate tumor response will be performed at baseline and at regular intervals during the study, as per RECIST v1.1 criteria.  
• Response Evaluation: Tumor response will be categorized as complete response, partial response, stable disease, or progressive disease.  
Safety Assessments  
• Adverse Events: All adverse events will be monitored, recorded, and graded according to the Common Terminology Criteria for Adverse Events (CTCAE).  
• Laboratory Tests: Routine blood tests, including complete blood count and chemistry panels, will be conducted to monitor for treatment-related toxicities.  
Pharmacokinetic/Pharmacodynamic Assessments  
• Blood Sampling: Pharmacokinetic (PK) samples will be collected at specified time points to assess the drug's pharmacokinetics.  
• Biomarker Analysis: Pharmacodynamic markers may be evaluated in blood or tumor samples, if applicable.  
Study Visits  
Schedule of Visits  
• Baseline Visit: Prior to the start of treatment, patients will undergo a comprehensive evaluation to establish baseline characteristics.  
• Treatment Visits: During each cycle, patients will visit the clinic for infusion and monitoring.  
• Follow-Up Visits: After the completion of treatment, patients will have follow-up visits to assess long-term outcomes and any late-emerging toxicities.  
Criteria for Discontinuation/Modification of Treatment  
Discontinuation Criteria  
• Disease Progression: Treatment will be discontinued upon evidence of disease progression.  
• Toxicity: Unacceptable toxicity, despite dose adjustments, will lead to treatment discontinuation.  
• Patient Decision: Patients may choose to discontinue treatment at any time.  
• Investigator Judgment: The investigator may discontinue treatment if deemed in the best interest of the patient.  
Treatment Modification  
• Toxicity Management: Specific guidelines for treatment modification in response to toxicities will be followed.  
• Dose Delays: Treatment may be delayed to allow recovery from adverse events.  
• Dose Reductions: Dose reductions may be implemented according to predefined criteria.  
Data Collection and Management  
Data Collection  
• Case Report Forms (CRFs): Data will be collected using standardized CRFs.  
• Electronic Data Capture (EDC): An EDC system will be utilized for data entry and management.  
Data Quality Assurance  
• Monitoring: Regular monitoring will be conducted to ensure data accuracy and protocol compliance.  
• Audits: Periodic audits may be performed to assess the quality and integrity of the study data.  
Ethical Considerations  
Informed Consent  
• Process: All patients will provide informed consent before participating in the study.  
• Documentation: Consent forms will detail the study procedures, risks, benefits, and patient rights.  
Institutional Review Board (IRB)/Ethics Committee (EC) Approval  
• Approval: The study protocol, consent forms, and any amendments will be approved by an IRB/EC.  
• Compliance: The study will be conducted in compliance with the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines, and local regulatory requirements.  
Post-Treatment Follow-Up  
Long-Term Follow-Up  
• Survival Tracking: Patients will be followed for overall survival after the completion of treatment.  
• Late Toxicity Assessment: Any late-emerging toxicities will be monitored and recorded.  
Study Completion  
• Final Assessment: A final assessment will be conducted to collect end-of-study data.  
• Study Closure: Upon study completion, all study documentation will be archived according to regulatory requirements.

8. Safety

Safety  
Overview of Safety Assessment  
The safety of amivantamab in patients with advanced colorectal cancer will be rigorously monitored throughout the study. The assessment of safety will be based on the incidence, severity, and type of adverse events (AEs), serious adverse events (SAEs), laboratory abnormalities, and any other clinically significant changes in health status.  
Adverse Event Monitoring and Reporting  
Definition of Adverse Events  
An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment.  
Collection and Documentation of Adverse Events  
All AEs experienced by the study participants will be collected and documented from the time of the first dose of study medication until 30 days after the last dose. AEs will be recorded in the patient's case report form (CRF) and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.  
Reporting of Serious Adverse Events  
SAEs, defined as any AE that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or causes a congenital anomaly/birth defect, must be reported to the sponsor within 24 hours of the site becoming aware of the event.  
Safety Assessments  
Physical Examinations  
Physical examinations will be conducted at baseline, at specified intervals during treatment, and at the end-of-treatment visit. Any new or worsening medical conditions will be recorded as AEs.  
Laboratory Assessments  
Routine laboratory assessments, including hematology, blood chemistry, and liver function tests, will be performed at baseline and at regular intervals throughout the study to monitor for potential treatment-related toxicities.  
Vital Signs and ECG Monitoring  
Vital signs will be measured at each visit, and electrocardiograms (ECGs) will be performed at baseline, during treatment, and at the end-of-treatment visit to detect any cardiac abnormalities.  
Management of Adverse Events  
Dose Modifications for Toxicity  
Dose modifications for amivantamab will be made in accordance with predefined criteria for specific AEs. The protocol will outline dose reduction levels, dose delays, and conditions under which treatment should be discontinued.  
Supportive Care  
Participants will receive appropriate supportive care for the management of AEs, including medications to prevent or treat symptoms, and other interventions as clinically indicated.  
Data Safety Monitoring  
Role of Investigators  
Investigators are responsible for the ongoing monitoring of the safety of study participants. They will promptly identify, treat, and report AEs and ensure that participants receive appropriate medical care.  
Safety Review Committee  
A Safety Review Committee (SRC) may be established to periodically review safety data and advise on safety-related matters. The SRC will consist of clinical experts who are independent of the study.  
Discontinuation of Study Treatment due to Adverse Events  
Participants may be discontinued from study treatment if they experience unacceptable AEs, as determined by the investigator or per the participant's request. The criteria for treatment discontinuation due to AEs will be clearly defined in the study protocol.  
Post-Study Safety Follow-Up  
Participants will be followed for 30 days after the last dose of study medication for the monitoring of any late-emerging AEs. Any SAEs occurring during this period will be reported to the sponsor.  
Safety Reporting to Regulatory Authorities  
All SAEs and other significant safety findings will be reported to regulatory authorities in accordance with local regulations and guidelines.  
Safety Analysis  
The safety analysis will include descriptive statistics of AEs and SAEs, including incidence, severity, timing, and relationship to the study drug. Safety data will be summarized for the safety population, which includes all patients who receive at least one dose of amivantamab.  
The safety results will be included in interim and final study reports and will be considered in the context of the study's benefit-risk assessment.