Clinical Trial Protocol

Title

Title Section

Study 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.

Background

Background

Colorectal Cancer

Prevalence and Mortality
Colorectal cancer (CRC) is one of the most common malignancies worldwide and a leading cause of cancer-related deaths. The disease is often diagnosed at an advanced stage, which significantly reduces the chances of survival. Despite advances in screening and treatment, the prognosis for patients with metastatic colorectal cancer remains poor.

Current Treatment Landscape
The standard of care for advanced colorectal cancer typically involves chemotherapy, targeted therapy, and immunotherapy. However, the effectiveness of these treatments is limited, especially in patients who have progressed on standard therapies. There is a significant unmet need for novel treatments that can improve outcomes for these patients.

EGFR and MET Pathway Alterations in CRC
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. These alterations can confer resistance to existing therapies and are associated with a poor prognosis. Targeting these pathways could provide a new therapeutic strategy for patients with these genetic profiles.

Rationale for Amivantamab in CRC
Amivantamab is a bispecific antibody that simultaneously targets EGFR and MET, designed to inhibit the signaling pathways that drive tumor growth and survival. The drug has shown promise in non-small cell lung cancer (NSCLC) patients with EGFR and MET alterations, suggesting potential applicability in other cancers with similar genetic alterations.

Study Justification
Given the limited treatment options for advanced colorectal cancer patients with EGFR and MET alterations and the demonstrated efficacy of amivantamab in NSCLC, there is a strong rationale for investigating the safety and efficacy of amivantamab in this patient population. This Phase 2 study will provide important data on the potential role of amivantamab as a treatment for advanced colorectal cancer.

Objectives

1. Objectives

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

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

Study Design

Study Design

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) who have documented EGFR and MET pathway alterations. The study will involve the administration of amivantamab intravenously at the recommended Phase 2 dose on Day 1 of each 21-day cycle.

Study Population

The study will enroll adults aged 18 years or older who have advanced or metastatic colorectal cancer with confirmed EGFR and MET alterations. Eligible participants must have shown progression on or after standard therapy, or for whom no standard treatment options are available.

Treatment Administration

Patients will receive the study drug, amivantamab, via intravenous infusion. The dosing schedule will be on Day 1 of each 21-day cycle, with dose adjustments made based on patient tolerance and any observed toxicity.

Duration of Treatment

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

Study Assessments

Efficacy assessments will include measurements of tumor response using RECIST criteria, while safety assessments will involve 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 safety profile of amivantamab.

Statistical Analysis

The study will enroll approximately 100 patients to ensure adequate power to detect a clinically meaningful difference in the ORR. Secondary analyses will focus on PFS, OS, and DCR, as well as safety data.

Study Duration

The estimated duration of the study is 24 months, which includes the time from the first patient enrollment to the completion of final data analysis. This timeline is subject to change based on enrollment rates and other factors.

Ethics and Patient Safety

The study will be conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and all applicable regulatory requirements. An independent data monitoring committee will oversee patient safety and treatment efficacy data throughout the study. All participants will provide written informed consent before any study-related procedures are performed.

Population

5. Population

5.1 Inclusion Criteria

• Age and Condition

Participants must be adults aged 18 years or older diagnosed with advanced or metastatic colorectal cancer.
• Genetic Alterations: Patients must have documented alterations in the EGFR and MET pathways, as these are the targets of amivantamab.
• Treatment History: Eligible patients should have experienced disease progression on or after standard therapy, or must be individuals for whom no standard treatment options are available.
• Consent: All participants must provide written informed consent prior to enrollment in the study.

5.2 Exclusion Criteria

• Prior Therapy

Patients who have received previous treatment with any drug specifically targeting EGFR and MET pathways within a certain timeframe before the start of the study may be excluded.
• Comorbid Conditions: Individuals with significant comorbidities or conditions that

could interfere with the study drug or assessments, or pose a risk to patient safety, may be excluded.
• Performance Status: Patients with a performance status that indicates severe disability or inability to care for oneself may not be eligible.
• Laboratory Values: Patients must meet certain laboratory criteria to ensure adequate organ function and minimize risks associated with treatment.
• Concurrent Conditions: Patients with active infections, significant cardiovascular disease, or other serious illnesses may be excluded.
• Pregnancy and Breastfeeding: Women who are pregnant or breastfeeding, or individuals (of any gender) not willing to use effective contraception during the study period, may be excluded due to potential risks to a fetus or infant.

5.3 Recruitment and Screening
• Recruitment Strategies: Patients will be recruited from oncology clinics, hospitals, and through patient registries that focus on colorectal cancer. Outreach may also include social media and patient advocacy groups.
• Screening Procedures: Potential participants will undergo a screening process that includes a review of medical history, physical examination, laboratory tests, and confirmation of EGFR and MET alterations through genetic testing.

5.4 Sample Size
• Total Enrollment

The study aims to enroll approximately 100 patients, which is determined to be sufficient to provide adequate power for detecting a clinically meaningful objective response rate (ORR) and to conduct secondary analyses for survival endpoints.

5.5 Ethical Considerations
• Informed Consent

Participants will receive detailed information about the study, including potential risks and benefits, and must provide written informed consent.
• Confidentiality: Patient confidentiality will be maintained throughout the study, with data anonymized as required by regulations.

5.6 Study Withdrawal
• Discontinuation Criteria

Patients may be withdrawn from the study if they experience unacceptable toxicity, disease progression, withdrawal of consent, or if the investigator deems it in the best interest of the patient.
• Follow-Up: Patients who withdraw from the study will be followed up as per the study protocol to capture data on safety and any long-term effects.

Procedures

6. Procedures

6.1 Treatment Administration Procedures

Initial Treatment Dose and Administration

- Patients will receive the initial dose of amivantamab intravenously on Day 1 of Cycle 1.
- The infusion will be administered over a period determined by the patient's tolerance and the prescribing information for amivantamab.
- Premedication may be administered as per protocol to mitigate infusion-related reactions.

Subsequent Treatment Cycles

- Subsequent doses of amivantamab will be administered on Day 1 of each 21-day cycle.
- Dose adjustments, including dose interruptions or reductions, will be made based on individual patient tolerance and in accordance with the study protocol.

Treatment Duration

- Treatment will continue until disease progression, unacceptable toxicity, withdrawal of consent, or other discontinuation criteria are met.

6.2 Monitoring Procedures

During Treatment

- Patients will be monitored during each infusion for signs of infusion-related reactions or other adverse events.
- Vital signs will be measured pre- and post-infusion.

Routine Monitoring

- Physical examinations, performance status evaluations, and routine laboratory tests will be conducted at specified intervals throughout the study.
- Adverse events will be monitored continuously and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE).

Efficacy Assessments

- Tumor measurements will be conducted at baseline and at specified intervals using RECIST criteria to assess response to treatment.
- Imaging studies will be performed to evaluate tumor response and disease progression.

6.3 Response Assessment Procedures

Objective Response Rate (ORR)

- ORR will be determined by the proportion of patients achieving complete response (CR) or partial response (PR) as per RECIST criteria.

Progression-Free Survival (PFS) and Overall Survival (OS)

- PFS will be measured from the start of treatment until the time of documented disease progression or death from any cause.
- OS will be measured from the start of treatment until death from any cause.

Disease Control Rate (DCR)
• DCR will be calculated as the sum of CR, PR, and stable disease (SD) rates.

6.4 Safety Assessment Procedures

Adverse Event Reporting
• All adverse events will be documented and reported in accordance with regulatory requirements and the study protocol.
• Serious adverse events (SAEs) will be reported to the regulatory authorities and the ethics committee as per regulatory guidelines.

Laboratory Assessments
• Blood samples will be collected for routine hematologic and biochemical laboratory assessments to monitor organ function and detect potential drug-related toxicities.

6.5 Data Collection and Management

Data Collection
• Data will be collected using case report forms (CRFs) designed for this study.
• Electronic data capture (EDC) systems may be used for data entry and management.

Data Quality Assurance
• Data will be reviewed regularly for completeness, accuracy, and consistency.
• Queries will be generated for missing or inconsistent data and resolved in a timely manner.

Data Analysis
• Data will be analyzed as per the statistical analysis plan (SAP) detailed in the protocol.
• Interim analyses may be conducted as specified in the study protocol.

6.6 Study Completion and Follow-Up Procedures

End of Treatment
• Upon discontinuation of treatment, patients will undergo an end-of-treatment visit, which includes a final assessment of tumor response, safety evaluations, and collection of any outstanding data.

Post-Treatment Follow-Up
• Patients will be followed up for a specified period post-treatment to collect data on long-term safety and survival outcomes.
• The schedule for follow-up visits and assessments will be outlined in the study protocol.

Study Close-Out
• Upon completion of the study, all study sites will undergo close-out procedures.
• Final data will be analyzed, and study results will be prepared for dissemination to the scientific community.

Statistical Analysis

7. Statistical Analysis

7.1 Overview of Statistical Analysis
The statistical analysis plan (SAP) for this Phase 2 study of amivantamab in patients with advanced colorectal cancer will detail the methods for evaluating the primary and secondary endpoints, handling of missing data, and the pre-specified statistical tests to be used.

7.2 Sample Size Determination
Based on preliminary data and assumptions regarding the expected objective response rate (ORR), a total of 100 patients will be enrolled to ensure adequate power to detect a clinically meaningful difference in ORR. Power calculations were performed considering the anticipated effect size, alpha level, and study design.

7.3 Analysis Populations
The analysis will include the following populations:
• Intent-to-treat (ITT) Population: All 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 will be included in the safety analyses.
• Per-protocol Population: Patients who complete the study without major protocol deviations will be included in the per-protocol analyses.

7.4 Primary Efficacy Analysis
The primary endpoint, ORR, will be calculated as the proportion of patients achieving a complete response (CR) or partial response (PR) as per RECIST criteria. The exact binomial method will be used to calculate the 95% confidence interval (CI) for the ORR.

7.5 Secondary Efficacy Analyses
• Progression-Free Survival (PFS): PFS will be analyzed using the Kaplan-Meier method, with the median PFS and its 95% CI estimated. The log-rank test will be used to compare PFS across subgroups, if applicable.
• Overall Survival (OS): OS will also be analyzed using the Kaplan-Meier method, with median OS and its 95% CI estimated.
• Disease Control Rate (DCR): DCR will be calculated as the sum of CR, PR, and stable disease (SD) rates, with the corresponding 95% CI estimated using the exact binomial method.

7.6 Safety Analysis
Adverse events will be summarized by frequency and severity, using the Common Terminology Criteria for Adverse Events (CTCAE). Serious adverse events (SAEs) and adverse events leading to discontinuation will be reported separately.

7.7 Interim Analysis
An interim analysis may be conducted for early assessment of safety and efficacy.

The timing and stopping rules for the interim analysis will be pre-specified in the SAP.

7.8 Handling of Missing Data
The approach to handling missing data will be specified in the SAP. Sensitivity analyses may be conducted to assess the impact of missing data on the study results.

7.9 Statistical Software
All statistical analyses will be performed using a validated statistical software package, as specified in the SAP.

7.10 Multiplicity
Adjustments for multiplicity will be considered in the analysis of secondary endpoints to control the overall type I error rate.

7.11 Subgroup Analyses
Exploratory subgroup analyses may be performed based on baseline characteristics and other relevant factors to investigate consistency of treatment effects.

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

7.13 Statistical Significance
All tests will be two-sided, with a significance level set at 0.05, unless otherwise specified in the SAP.

7.14 Reporting of Results
Results will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines and will include point estimates, 95% confidence intervals, and p-values for all primary and secondary endpoints.

Safety

8. Safety

8.1 Safety Monitoring

Safety monitoring will be a continuous process throughout the study, with the collection and evaluation of adverse events (AEs), serious adverse events (SAEs), laboratory abnormalities, and other safety-related outcomes. The study will employ the Common Terminology Criteria for Adverse Events (CTCAE) for the classification and grading of AEs.

8.2 Adverse Event Reporting

All AEs observed during the study or reported by participants will be recorded, regardless of suspected causality. Investigators will document the onset, duration, severity, resolution, and any actions taken in response to the AE. SAEs will be

reported immediately to the study sponsor, the ethics committee, and regulatory authorities as per regulatory guidelines.

8.3 Infusion-Related Reactions

Given that amivantamab is administered intravenously, there is a potential for infusion-related reactions. Patients will be monitored closely during and after each infusion. Premedication and post-medication protocols will be in place to manage any such reactions.

8.4 Dose Adjustments and Discontinuation

Dose adjustments for amivantamab will be made in the event of AEs, according to predefined criteria. Treatment may be interrupted, reduced, or discontinued depending on the severity and persistence of AEs.

8.5 Safety Assessments

Safety assessments will include

• Routine physical examinations
• Monitoring of vital signs
• Electrocardiograms (ECGs)
• Routine laboratory tests for hematology, biochemistry, and organ function

8.6 Data Safety Monitoring Board (DSMB)

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

8.7 Patient Safety and Ethics

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and will adhere to Good Clinical Practice (GCP) guidelines. An Ethics Committee (EC) will review and approve the study protocol and any amendments.

8.8 Informed Consent

Participants will be fully informed of the potential risks and benefits of the study. Informed consent will be obtained from all participants before enrollment and before any study-related procedures are carried out.

8.9 Emergency Procedures

Emergency contact information will be provided to participants for reporting AEs occurring outside of study visits. Study staff will be trained to respond to emergencies and ensure appropriate medical care for participants.

8.10 Handling of Adverse Events

A protocol for the management of AEs, including dose modification and discontinuation rules, will be detailed in the study protocol. Investigators will be trained on this protocol to ensure consistent handling of AEs across study sites.

8.11 Reporting of Long-Term Adverse Effects

Participants will be followed for a specified period post-treatment to monitor for any long-term adverse effects related to the study drug. The nature and frequency of follow-up visits and assessments will be outlined in the study protocol.

8.12 Record Keeping and Documentation

All safety information will be documented in the participant's medical record and in the study records. Adequate record keeping will be ensured for auditing purposes and for the verification of data collected during the study.

8.13 Study Discontinuation Criteria

Criteria for the discontinuation of the study due to safety concerns will be predefined and may include a specific frequency or severity of AEs, SAEs, or other safety signals identified by the DSMB or regulatory authorities.