Clinical Trial Protocol

Background

Background & Rationale

Colorectal cancer (CRC) is a significant public health concern and a leading cause of cancer-related deaths worldwide. Despite advances in screening and treatment, patients with advanced-stage CRC have a poor prognosis. The five-year survival rate for metastatic CRC is approximately 14%, underscoring the urgent need for novel therapeutic strategies.

The epidermal growth factor receptor (EGFR) and the mesenchymal-epithelial transition (MET) factor have been identified as critical drivers of CRC progression. Alterations in these pathways contribute to tumor growth, metastasis, and resistance to therapy. Current treatments targeting EGFR have shown limited efficacy, and resistance often develops through secondary mutations or activation of bypass signaling pathways, such as MET.

Amivantamab is a bispecific antibody designed to simultaneously inhibit both the EGFR and MET signaling pathways. This dual targeting approach has the potential to overcome resistance mechanisms and provide a new treatment option for patients with CRC harboring alterations in these pathways. In non-small cell lung cancer (NSCLC), amivantamab has demonstrated promising efficacy and a manageable safety profile, suggesting its potential applicability in other EGFR and MET-driven cancers.

Given the unmet medical need for effective treatments in advanced CRC and the promising preclinical and clinical data for amivantamab in NSCLC, this Phase 2 study will evaluate the safety and efficacy of amivantamab in patients with advanced colorectal cancer with EGFR and MET alterations. The study will provide important insights into the therapeutic value of amivantamab in this patient population and inform future clinical development.

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 receiving amivantamab therapy.
• To measure the disease control rate (DCR) in the study population.

• To characterize the safety and tolerability profile of amivantamab in this patient cohort.

Study Design

Study Design

Overview

This 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) that exhibit alterations in the EGFR and MET pathways. The study will involve the administration of amivantamab intravenously at the recommended Phase 2 dose, with treatment cycles repeating every 21 days.

Study Population

The study will enroll adults aged 18 or older diagnosed with advanced or metastatic CRC. Eligible 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.

Treatment Administration

Participants will receive amivantamab via intravenous infusion on Day 1 of each 21-day cycle. The dosing will be based on the recommended Phase 2 dose, with dose adjustments made according to patient tolerance and in response to any observed adverse events.

Duration of Treatment

Treatment will continue until disease progression, unacceptable toxicity, withdrawal of consent, or other criteria for discontinuation are met. Patients will be followed for response to therapy, progression of disease, and survival.

Study Assessments

Assessments will be conducted at baseline, at specified intervals during treatment, and at the end of treatment or upon early discontinuation. These assessments will include imaging studies to evaluate tumor response, laboratory tests for safety monitoring, and patient-reported outcomes to assess quality of life.

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 defined by the Common Terminology Criteria for Adverse Events (CTCAE).

Statistical Analysis

The study will include a sample size of 100 patients, which is estimated to provide sufficient power to detect a clinically meaningful difference in the primary endpoint of ORR. Secondary analyses will focus on PFS, OS, and DCR, as well as safety and tolerability data.

Study Timeline

The estimated duration of the study is 24 months, which includes the time from the start of enrollment to the completion of final data analysis. The timeline may be adjusted based on actual enrollment rates and data collection progress.

Population

5. Population

5.1 Inclusion Criteria

1. Age and Condition

Adults aged 18 years or older diagnosed with advanced or metastatic colorectal cancer (CRC).
2. Genetic Alterations: Documented alterations in the EGFR and MET pathways, confirmed by a validated molecular assay.
3. Disease Progression: Patients must have experienced disease progression on or after standard therapy, or must be patients for whom no standard treatment options are available.
4. Performance Status: An Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.
5. Adequate Organ Function: Sufficient hepatic, renal, and hematologic function as defined by protocol-specific laboratory criteria.
6. Informed Consent: Ability to understand and willingness to sign a written informed consent document.

5.2 Exclusion Criteria

1. Prior Therapy

Patients who have received prior treatment with any drug specifically targeting EGFR and/or MET for their colorectal cancer.
2. Concurrent Conditions: Presence of any serious or uncontrolled medical disorder, nonmalignant systemic disease, or active, uncontrolled infection.
3. Brain Metastases: Patients with symptomatic brain metastases or leptomeningeal disease.

4. Other Malignancies: History of another primary malignancy that has not been in remission for at least 3 years.
5. Pregnancy: Pregnant or breastfeeding women, due to the potential for congenital abnormalities and the potential of this regimen to harm nursing infants.
6. Allergies: Known hypersensitivity to any component of amivantamab or similar compounds.

5.3 Withdrawal Criteria

Patients may withdraw from the study for any of the following reasons:

1. Voluntary Withdrawal

Patient's decision to withdraw at any time for any reason.
2. Adverse Events: The occurrence of intolerable grade 3 or 4 adverse events, despite appropriate medical management.
3. Noncompliance: Noncompliance with the study protocol or treatment regimen.
4. Investigator Judgment: At the discretion of the investigator for reasons including but not limited to safety, protocol violation, or administrative reasons.

5.4 Replacement of Participants

Participants who withdraw from the study will be replaced to ensure that the study meets its intended sample size of 100 patients. Replacement will occur in accordance with the inclusion and exclusion criteria and will be documented appropriately.

Procedures

6. Procedures

6.1 Screening Procedures

Prior to enrollment, potential participants will undergo a screening process to confirm eligibility. Screening will include:
• Informed consent review and signing
• Medical history and physical examination
• Performance status evaluation
• Documentation of EGFR and MET pathway alterations
• Baseline tumor imaging using CT or MRI
• Laboratory tests to assess organ function
• Pregnancy test for women of childbearing potential

Screening must be completed within 28 days prior to the first dose of study medication.

6.2 Enrollment

Eligible patients who consent to participate and meet all inclusion criteria will be enrolled in the study. Enrollment will be documented, and patients will be assigned a unique study identification number.

6.3 Treatment Administration
• Amivantamab will be administered intravenously on Day 1 of each 21-day cycle.
• Premedication may be given to mitigate infusion-related reactions.
• The initial dose will be based on the recommended Phase 2 dose, with subsequent doses adjusted according to individual patient tolerance and safety.
• Treatment will continue until disease progression, unacceptable toxicity, withdrawal of consent, or other discontinuation criteria are met.

6.4 Safety and Efficacy Assessments
• Tumor assessments will be performed every 6 weeks for the first 24 weeks, then every 9 weeks thereafter, or as clinically indicated.
• Adverse events will be monitored continuously and graded according to CTCAE criteria.
• Laboratory tests for safety monitoring will be conducted at the beginning of each cycle and as needed.
• Efficacy will be assessed through imaging studies and RECIST 1.1 criteria for tumor response.

6.5 Study Visits

Patients will attend study visits on Day 1 of each cycle for treatment administration, safety assessments, and to review any adverse events. Additional visits may be scheduled as needed for efficacy assessments or to manage adverse events.

6.6 Concomitant Medications
• All concomitant medications and supportive care measures will be documented throughout the study.
• Medications with known significant interactions with amivantamab will be avoided.

6.7 Post-Treatment Follow-Up

After discontinuation of treatment, patients will be followed for long-term outcomes, including:
• Survival status every 12 weeks until death, withdrawal of consent, or the end of the study.
• Post-study treatment for cancer, if applicable.

6.8 Data Collection and Management

Data will be collected using electronic case report forms (eCRFs). All data will be de-identified to protect patient confidentiality. Data management procedures will ensure accuracy, completeness, and reliability of the study data.

6.9 Study Completion and Close-Out

The study will be considered complete when the last patient completes the final study visit or the study is terminated. A close-out visit will be conducted at each study site to ensure all data are collected and all study-related materials are accounted for.

Statistical

7. Statistical Analysis

7.1 General Considerations
Statistical analysis for this Phase 2 study will be performed using the intent-to-treat (ITT) population, which includes all patients who received at least one dose of amivantamab. The primary analysis will focus on the primary endpoint, with secondary endpoints analyzed in a hierarchical manner to control for type I error due to multiple testing.

7.2 Primary Endpoint Analysis
The primary endpoint, objective response rate (ORR), will be calculated as the proportion of patients achieving a complete response (CR) or partial response (PR), as defined by RECIST 1.1 criteria. The exact binomial method will be used to construct 95% confidence intervals (CIs) for the ORR.

7.3 Secondary Endpoint Analysis
Secondary endpoints, including progression-free survival (PFS), overall survival (OS), and disease control rate (DCR), will be analyzed using Kaplan-Meier methods. Median PFS and OS will be estimated with corresponding 95% CIs. The DCR will be calculated as the proportion of patients achieving CR, PR, or stable disease (SD), with 95% CIs constructed using the exact binomial method.

7.4 Safety Analysis
Safety will be assessed by the incidence and severity of adverse events (AEs), graded according to the Common Terminology Criteria for Adverse Events (CTCAE). Descriptive statistics will summarize the AEs, serious adverse events (SAEs), and AEs leading to discontinuation.

7.5 Sample Size Justification
The sample size of 100 patients is based on assumptions about the expected ORR and the precision of the estimate. This sample size is considered sufficient to estimate the ORR with a two-sided 95% confidence interval that provides a clinically meaningful precision.

7.6 Interim Analysis
An interim analysis may be conducted for safety evaluation by an independent data monitoring committee (IDMC) after a pre-specified number of patients have been treated and assessed for safety. The IDMC will have the authority to recommend modifications to the study, including early termination, if necessary.

7.7 Statistical Software
All statistical analyses will be performed using the latest version of a statistical software package, such as SAS or R, which is validated and compliant with regulatory guidelines.

7.8 Handling of Missing Data
Missing data will be handled using appropriate imputation methods, such as last

observation carried forward (LOCF) for efficacy endpoints. Sensitivity analyses will be conducted to assess the robustness of the results to the missing data assumptions.

7.9 Subgroup Analyses
Exploratory subgroup analyses may be performed to assess the consistency of treatment effects across various patient subgroups, such as age, sex, performance status, and baseline disease characteristics. These analyses will be considered hypothesis-generating and not definitive.

7.10 Multiplicity Considerations
Adjustments for multiple comparisons will be made using methods such as Bonferroni correction or false discovery rate (FDR) to control the overall type I error rate.

7.11 Data Monitoring and Ethics
The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. The IDMC will oversee the study's conduct and ensure the integrity of the data and the safety of the participants.

7.12 Reporting of Results
Results will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines for clinical trials. All significant findings, as well as any non-significant trends, will be reported in the final study publication.

Safety

8. Safety

8.1 Adverse Event Monitoring

All adverse events (AEs) will be monitored and recorded from the time of consent until 30 days after the last dose of amivantamab. AEs will be graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. The severity of AEs will be categorized as follows:
• Grade 1: Mild
• Grade 2: Moderate
• Grade 3: Severe
• Grade 4: Life-threatening
• Grade 5: Death related to AE

8.2 Serious Adverse Event Reporting

Serious adverse events (SAEs) will be reported to the appropriate regulatory authorities and ethics committees within 24 hours of the study team becoming aware of the event. An SAE is defined as any AE that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization,

results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

8.3 Management of Adverse Events

Participants experiencing AEs will receive appropriate medical management, including dose adjustments or treatment discontinuation if necessary. The protocol outlines specific management guidelines for infusion-related reactions, which are known to occur with monoclonal antibody treatments.

8.4 Dose Modification and Discontinuation Criteria

Dose modifications for amivantamab will be based on the type and severity of AEs. The protocol provides detailed instructions for dose reductions, treatment delays, and criteria for permanent discontinuation of the study drug.

8.5 Safety Assessments

Safety assessments will include physical examinations, vital signs, clinical laboratory tests (hematology, blood chemistry, and liver function tests), and documentation of all AEs and SAEs. Safety assessments will be conducted at baseline, on Day 1 of each treatment cycle, and at the end of treatment or upon early discontinuation.

8.6 Data Safety Monitoring Board (DSMB)

An independent Data Safety Monitoring Board (DSMB) will be established to periodically review accumulated study data for participant safety, study conduct, and progress. The DSMB will have the authority to recommend modifications to the study, including early termination, if necessary.

8.7 Reporting of Unanticipated Problems

All unanticipated problems involving risks to participants or others will be reported to the DSMB, regulatory authorities, and ethics committees as per regulatory requirements.

8.8 Patient Withdrawal Due to Adverse Events

Participants have the right to withdraw from the study at any time for any reason, including intolerable AEs. The procedures for withdrawal and post-withdrawal care are outlined in the protocol.

8.9 Post-Study Surveillance

Following the completion of the study, long-term follow-up for safety will be conducted as appropriate, based on the known safety profile of amivantamab and any emerging safety concerns during the study.

8.10 Safety Endpoint Analysis

The incidence and severity of AEs and SAEs will be summarized using descriptive statistics. The relationship of AEs to the study drug will be assessed and reported. Safety data will be reviewed in the context of the study's benefit-risk assessment.