Clinical Trial Protocol

Title

Protocol 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 one of the leading causes of cancer-related deaths worldwide. The prognosis for patients with advanced-stage disease remains poor, with few therapeutic options available once standard treatments have failed. Alterations in the epidermal growth factor receptor (EGFR) and the mesenchymal-epithelial transition (MET) pathways are known to contribute to the pathogenesis and progression of colorectal cancer. Amivantamab is a novel bispecific antibody that simultaneously targets both EGFR and MET, and has shown promise in the treatment of non-small cell lung cancer (NSCLC). Given the similarity in the molecular pathways involved, this Phase 2 study is designed to investigate the potential of amivantamab as a therapeutic option for patients with advanced colorectal cancer harboring these alterations.

Study Objectives

Primary Objective

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

Key Inclusion Criteria

• Adult patients (≥18 years of age) diagnosed with advanced or metastatic colorectal cancer.
• Molecular profiling confirming EGFR and MET pathway alterations.
• Disease progression following standard therapy, or patients for whom no standard treatment options are available.

Treatment Plan

Eligible patients will be administered amivantamab intravenously at the established recommended Phase 2 dose on Day 1 of each 21-day cycle. Dose adjustments will be made as necessary based on individual patient tolerance and safety

considerations.

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 defined 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 ORR. Secondary endpoints, including PFS and OS, will be analyzed using appropriate statistical methods.

Timeline

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

Background

Background & Rationale

Colorectal cancer (CRC) is a major cause of morbidity and mortality worldwide, ranking as the third most common cancer and the second leading cause of cancer-related deaths. The management of advanced CRC poses a significant clinical challenge, as patients frequently exhibit resistance to conventional chemotherapeutic agents and targeted therapies. The five-year survival rate for metastatic CRC remains low, underscoring the urgent need for novel therapeutic strategies.

Alterations in the epidermal growth factor receptor (EGFR) and the mesenchymal-epithelial transition (MET) pathways have been implicated in the pathogenesis of CRC. These genetic aberrations are associated with poor prognosis and may drive resistance to existing treatments. EGFR is a transmembrane tyrosine kinase receptor that, when overexpressed or mutated, can lead to uncontrolled cell proliferation. Similarly, aberrant activation of the MET pathway, often through overexpression or amplification of the MET gene, can promote tumor growth, angiogenesis, and metastasis.

Amivantamab is a first-in-class, fully human bispecific antibody that simultaneously targets both EGFR and MET receptors. By binding to these receptors, amivantamab is designed to inhibit their signaling and induce antibody-dependent cellular cytotoxicity, potentially overcoming the resistance mechanisms associated with each pathway. The efficacy of amivantamab has been demonstrated in non-small cell lung cancer (NSCLC), a malignancy that shares some molecular characteristics with CRC, particularly in terms of EGFR and MET alterations.

Given the success of amivantamab in NSCLC and the mechanistic rationale for its activity in CRC, this Phase 2 study aims to explore the therapeutic potential of amivantamab in patients with advanced CRC harboring EGFR and MET alterations. The study will provide critical data on the safety and efficacy of amivantamab in this

patient population, potentially offering a new treatment avenue for those with limited options.

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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 (CRC) with documented alterations in the epidermal growth factor receptor (EGFR) and the mesenchymal-epithelial transition (MET) pathways.

Study Population

The study will enroll adult patients (≥18 years of age) diagnosed with advanced or metastatic CRC. Eligible participants must have molecular profiling confirming EGFR and MET pathway alterations and must have experienced disease progression following standard therapy or have no available standard treatment options.

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 individual patient tolerance and safety considerations.

Duration

The study will have an estimated duration of 24 months, which includes the time for patient enrollment, treatment administration, follow-up, and final data analysis.

Study Assessments

Efficacy assessments will be conducted using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 to determine the objective response rate (ORR). Secondary efficacy assessments will include progression-free survival (PFS), overall survival (OS), and disease control rate (DCR). Safety will be monitored throughout the study, with adverse events graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Study Endpoints

The primary endpoint of the study is the ORR. Secondary endpoints include PFS, OS, DCR, and the incidence and severity of adverse events.

Statistical Analysis

Approximately 100 patients will be enrolled to ensure sufficient statistical power to detect a clinically meaningful difference in ORR. Secondary endpoints, such as PFS and OS, will be analyzed using appropriate statistical methods to evaluate the

therapeutic impact of amivantamab.

Ethical Considerations

The study will be conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines, and local regulatory requirements. An independent ethics committee or institutional review board will approve the study protocol. Informed consent will be obtained from all participants before any study-related procedures are conducted.

Study Oversight

A Data Monitoring Committee (DMC) will be established to periodically review safety data and ensure the integrity of the trial. The DMC will have the authority to recommend modifications, continuation, or termination of the study based on ongoing safety evaluations.

Population

Population

1 Inclusion Criteria

1. 1. Age and Condition

• Adult patients (≥18 years of age) diagnosed with advanced or metastatic colorectal cancer (CRC).

2. 2. Genetic Alterations

• Molecular profiling confirming alterations in the epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition (MET) pathways.

3. 3. Treatment History

• Disease progression following standard therapy, or for patients for whom no standard treatment options are available.

2 Exclusion Criteria

4. 1. Prior Therapy

• Patients who have received previous treatment with any drug specifically targeting EGFR or MET pathways within a specified timeframe before enrollment (to be defined based on pharmacokinetics and pharmacodynamics data).

5. 2. Comorbid Conditions

• Presence of any serious medical condition or psychiatric illness that could potentially interfere with the completion of treatment according to this protocol.

6. 3. Laboratory Values

• Abnormal laboratory values that suggest significant organ dysfunction, which may put the patient at risk if participating in the study (specific laboratory value thresholds will be detailed in the protocol).

7. 4. Concurrent Medications

• Use of any other investigational agents or concurrent anticancer therapy.

8. 5. Pregnancy and Breastfeeding

• Pregnant or breastfeeding women, due to the potential for adverse effects on the fetus or infant.

3 Recruitment and Screening

• Patients will be identified and recruited from oncology clinics and hospitals with access to molecular profiling for CRC.

• Screening will involve reviewing medical history, conducting physical examinations, and verifying eligibility through laboratory tests and genetic profiling.
4 Enrollment Procedures
• Eligible patients will be informed about the study details, including potential risks and benefits.
• Written informed consent will be obtained from all participants before enrollment.
• Baseline assessments will be conducted to ensure that all inclusion criteria are met and no exclusion criteria are present.
5 Withdrawal Criteria
• Participants may withdraw from the study at any time for any reason.
• The study protocol will outline specific criteria for withdrawal due to adverse events, lack of therapeutic effect, or protocol non-compliance.
6 Sample Size Determination
• The study aims to enroll approximately 100 patients to ensure sufficient statistical power to detect a clinically meaningful difference in the primary endpoint of ORR.
• The sample size takes into consideration potential dropouts and non-evaluable patients.
Procedures
Procedures
1 Treatment Administration
Patients will be administered amivantamab intravenously at the recommended Phase 2 dose on Day 1 of each 21-day cycle. The infusion will be performed in a clinical setting with appropriate medical support to manage potential infusion-related reactions.
1.1 Dosage Adjustments
Dose adjustments for amivantamab will be made in response to adverse events according to predefined criteria. Dose reductions, delays, or discontinuations will be considered based on the severity and type of adverse events experienced by the patient.
1.2 Concomitant Medications
Patients may receive supportive care medications as needed, including antiemetics, antipyretics, or analgesics. The use of concomitant medications will be documented throughout the study.
2 Efficacy Assessments
Efficacy assessments will be conducted at specified intervals to determine the objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and disease control rate (DCR).
2.1 Imaging Studies
Radiographic assessments will be performed using computed tomography (CT) or magnetic resonance imaging (MRI) at baseline and at regular intervals during the study to evaluate tumor response according to RECIST v1.1 criteria.
3 Safety Assessments
Safety will be continuously monitored throughout the study, with adverse events recorded and graded according to the Common Terminology Criteria for Adverse

Events (CTCAE) version 5.0.
3.1 Laboratory Tests
Routine blood tests, including complete blood count (CBC), liver function tests (LFTs), and renal function tests, will be conducted to monitor for potential drug-induced toxicity.
3.2 Physical Examinations
Regular physical examinations will be conducted to assess the overall health status of the patient and to detect any physical signs of adverse events.
4 Study Visits and Procedures
Patients will attend study visits on Day 1 of each cycle for treatment administration, efficacy assessments, safety assessments, and to address any concerns or symptoms they may have.
4.1 Initial Visit
At the initial visit, patients will undergo a comprehensive evaluation, including a review of their medical history, a physical examination, baseline imaging studies, and laboratory tests.
4.2 Follow-up Visits
Follow-up visits will occur at a minimum of every 21 days coinciding with the treatment cycles, with additional visits scheduled as needed for further assessment or management of adverse events.
5 Study Completion and Follow-up
Upon completion of the treatment phase, patients will enter a follow-up phase where they will be monitored for long-term efficacy and safety outcomes. The duration and frequency of follow-up visits will be outlined in the study protocol.
5.1 Post-Treatment Follow-up
Patients will be followed for survival status, subsequent cancer therapies, and long-term adverse events for a specified period after the end of treatment.
5.2 Data Collection and Management
All data collected during the study will be recorded in the case report forms (CRFs) and managed according to Good Clinical Practice (GCP) guidelines to ensure accuracy and confidentiality.
6 Discontinuation of Study Treatment
Patients may discontinue study treatment for reasons including, but not limited to, disease progression, unacceptable toxicity, patient withdrawal of consent, or at the investigator's discretion. Procedures for post-discontinuation care and follow-up will be specified in the protocol.
Statistical Analysis
Statistical Analysis
1 Overview
The statistical analysis plan for this Phase 2 study of amivantamab in patients with advanced colorectal cancer with EGFR and MET alterations will detail the methods used to evaluate the primary and secondary endpoints, handle missing data, perform subgroup analyses, and ensure the integrity of the data.
2 Primary Endpoint Analysis

The primary endpoint, objective response rate (ORR), will be calculated as the proportion of patients who achieve a complete or partial response according to RECIST v1.1 criteria. The 95% confidence interval (CI) for the ORR will be estimated using the exact binomial method.

3 Secondary Endpoint Analysis

Secondary endpoints, including progression-free survival (PFS), overall survival (OS), and disease control rate (DCR), will be analyzed as follows:

• PFS and OS: Kaplan-Meier methods will be used to estimate the median PFS and OS with corresponding 95% CIs. The log-rank test will be used to compare survival distributions if applicable.

• DCR: DCR will be calculated as the proportion of patients who achieve a complete response, partial response, or stable disease, with the 95% CI estimated using the exact binomial method.

4 Safety Analysis

Adverse events will be summarized by frequency and severity, using descriptive statistics. Incidence rates of adverse events will be compared to historical controls if available.

5 Interim Analysis

An interim analysis may be conducted for safety and futility once a pre-specified number of patients have been followed for a minimum duration. The stopping guidelines will be defined by the Data Monitoring Committee (DMC) based on the severity of adverse events and lack of efficacy.

6 Handling of Missing Data

Missing data will be handled using the last observation carried forward (LOCF) approach for efficacy analyses. Sensitivity analyses will be conducted to assess the impact of missing data on the study results.

7 Subgroup Analysis

Subgroup analyses will be performed to explore the consistency of treatment effects across various patient subgroups, including but not limited to, age, gender, and baseline disease characteristics. These analyses will be exploratory in nature and not powered to detect statistical significance.

8 Sample Size Justification

The sample size of 100 patients is based on assumptions about the expected ORR and the precision of the estimate required. This sample size is deemed sufficient to provide a precise estimate of the ORR, with allowance for a dropout rate of up to 10%.

9 Statistical Software

All statistical analyses will be performed using the latest version of SAS (Statistical Analysis System) or an equivalent statistical software package.

10 Significance Level

All tests of hypotheses will be two-sided with a significance level set at 0.05, unless otherwise specified.

11 Protocol Deviations

Protocol deviations will be summarized and their potential impact on the study

results will be assessed.
12 Data Review and Quality Assurance
Data will be reviewed regularly to ensure accuracy and completeness. Quality assurance procedures will be in place to maintain the integrity of the trial data.
13 Reporting of Results
The results of the statistical analyses will be reported in accordance with the CONSORT guidelines for clinical trials. All primary and secondary endpoints, as well as safety outcomes, will be included in the final report.
14 Ethical Considerations
All statistical analyses will be conducted respecting the confidentiality and anonymity of the study participants. The analysis plan will be approved by the appropriate regulatory and ethics committees prior to implementation.
Safety
Safety
1 Safety Monitoring
Safety will be monitored continuously throughout the study. Adverse events (AEs) will be recorded and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Serious adverse events (SAEs) will be reported to the regulatory authorities, ethics committees, and the Data Monitoring Committee (DMC) as per regulatory requirements.
2 Adverse Event Management
Patients will be monitored for signs and symptoms of AEs during each study visit. Management of AEs may include dose adjustments, treatment delays, or discontinuation of study treatment. Supportive care will be provided as needed to manage symptoms.
2.1 Dose Adjustments
Dose adjustments for amivantamab will be made in response to AEs as per predefined criteria. The criteria for dose reduction or interruption will be detailed in the study protocol.
2.2 Treatment Discontinuation
Study treatment may be discontinued due to unacceptable toxicity, patient withdrawal of consent, disease progression, or at the investigator's discretion. Procedures for managing treatment discontinuation and follow-up care will be outlined in the study protocol.
3 Infusion-Related Reactions
Given that amivantamab is administered intravenously, there is a potential for infusion-related reactions. Pre-medications and post-infusion monitoring will be implemented to mitigate and manage such reactions.
4 Laboratory Monitoring
Routine blood tests, including complete blood count (CBC), liver function tests (LFTs), and renal function tests, will be conducted to monitor for potential drug-induced toxicity. Any laboratory abnormalities will be managed according to the study protocol.
5 Safety Assessments

Safety assessments will include regular physical examinations, vital sign measurements, and the monitoring of AEs and SAEs. The frequency and nature of these assessments will be detailed in the study protocol.

6 Data Monitoring Committee (DMC)

A DMC will be established to periodically review safety data and ensure the integrity of the trial. The DMC will have the authority to recommend modifications, continuation, or termination of the study based on ongoing safety evaluations.

7 Reporting of Adverse Events

All AEs and SAEs will be reported in a timely manner to the sponsor, regulatory authorities, and ethics committees as required. The reporting procedures will comply with local regulations and the study protocol.

8 Patient Education

Patients will be educated on the potential risks and signs of AEs associated with amivantamab. They will be instructed to report any new or worsening symptoms to the study team immediately.

9 Emergency Procedures

Emergency contact information and procedures will be provided to patients in case of urgent health issues related to the study treatment. Study sites will have protocols in place to manage medical emergencies.

10 Safety Endpoints

The safety endpoints of the study will include the incidence, severity, and type of AEs, time to onset and resolution of AEs, and any dose modifications due to AEs. These will be summarized using descriptive statistics and compared to historical data if available.

11 Interim Safety Analysis

An interim safety analysis may be conducted by the DMC to assess the risk-benefit ratio of the study treatment. The criteria for interim analysis and potential study modifications will be predefined in the study protocol.

12 Ethical Considerations

The safety and well-being of study participants will be the foremost priority. The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and Good Clinical Practice guidelines.

13 Informed Consent Process

Informed consent will be obtained from all participants before any study-related procedures are conducted. The consent form will include detailed information about the study, including potential risks and AEs associated with amivantamab.