Clinical Trial Protocol

Title

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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 a leading cause of cancer-related mortality worldwide. The prognosis for patients with advanced-stage colorectal cancer remains poor, with few effective treatment options available, especially for those whose tumors harbor alterations in the EGFR and MET signaling pathways. Amivantamab is a novel bispecific antibody that simultaneously targets both the EGFR and MET receptors and has shown promising results in the treatment of non-small cell lung cancer (NSCLC). The rationale for this study is to investigate the potential of amivantamab to provide a new therapeutic option for patients with colorectal cancer who have limited treatment choices due to specific genetic alterations in their tumors.

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 the study population.
• To determine the disease control rate (DCR) in patients receiving amivantamab.
• 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 documented EGFR and MET pathway alterations.

Key Inclusion Criteria

• Adult patients (≥18 years) diagnosed with advanced or metastatic colorectal cancer.
• Genetic confirmation of EGFR and MET pathway alterations in tumor tissue.
• Disease progression following standard therapy, or 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 to the treatment.

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 as measures of safety and tolerability.
Statistical Considerations
The study aims to enroll a total of 100 patients, which is calculated to provide sufficient statistical power to detect a clinically meaningful difference in the primary endpoint of ORR. Secondary endpoints related to survival will also be analyzed.
Timeline
The estimated duration of the study is 24 months, which includes the time from the start of patient enrollment to the completion of final data analysis.
Background
Background & Rationale
Colorectal cancer (CRC) is a major cause of cancer-related deaths globally, with the prognosis for patients with advanced-stage disease being particularly poor. Standard treatments for advanced CRC are often ineffective, leaving a substantial unmet need for novel therapeutic options. This is especially true for patients whose tumors exhibit alterations in the epidermal growth factor receptor (EGFR) and the hepatocyte growth factor receptor (MET) pathways, which are known to contribute to tumor growth and resistance to therapy.
Amivantamab is a first-in-class, fully human bispecific antibody that targets both EGFR and MET receptors. By inhibiting these pathways, amivantamab has the potential to impede tumor growth and overcome resistance mechanisms. Its efficacy has already been observed in non-small cell lung cancer (NSCLC), where it has shown promising results in patients with EGFR and MET alterations.
Given the success of amivantamab in NSCLC and the mechanistic similarities in the role of EGFR and MET in CRC, there is a strong rationale to investigate the efficacy and safety of amivantamab in the treatment of advanced colorectal cancer. This Phase 2 study is designed to fill the gap in treatment options for CRC patients with specific genetic alterations that make them suitable candidates for targeted therapy with amivantamab.
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Overview

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Study Population

The study will enroll adult patients (≥18 years) diagnosed with advanced or metastatic colorectal cancer who have genetic confirmation of EGFR and MET pathway alterations in their tumor tissue. Eligible participants must have experienced disease progression following standard therapy, or for whom no standard treatment options are available.

Intervention

Participants will receive amivantamab administered 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 to the treatment.

Duration of Treatment

Patients will continue to receive treatment until disease progression, unacceptable toxicity, withdrawal of consent, or other criteria for discontinuation are met.

Study Assessments

Tumor assessments will be conducted using RECIST v1.1 criteria at baseline and at regular intervals during treatment to evaluate response. Safety assessments, including the monitoring of adverse events, will be conducted throughout the study.

Study Duration

The estimated duration of the study is 24 months, which includes the time from the start of patient enrollment to the completion of final data analysis.

Study Endpoints

The primary endpoint of the study is the objective response rate (ORR). Secondary endpoints include progression-free survival (PFS), overall survival (OS), disease control rate (DCR), and the incidence and severity of adverse events.

Statistical Considerations

The study aims to enroll a total of 100 patients, which is calculated to provide sufficient statistical power to detect a clinically meaningful difference in the primary endpoint of ORR. Secondary endpoints related to survival will also be analyzed.

Population

Population

1 Inclusion Criteria

1. 1. Age and Condition

Adult patients (≥18 years) diagnosed with advanced or metastatic colorectal cancer.

Genetic Alterations: Documented EGFR and MET pathway alterations in tumor tissue, as confirmed by a validated molecular assay.

Treatment History: Patients must have experienced disease progression on or after standard therapy, or must be patients for whom no standard treatment options are available.

Performance Status: Patients must have an Eastern Cooperative Oncology Group

(ECOG) performance status of 0-1.
Adequate Organ Function: Patients must have adequate renal, hepatic, and hematologic function as defined by protocol-specific criteria.
Informed Consent: Ability to understand and the willingness to sign a written informed consent document.
2 Exclusion Criteria
2. 1. Prior Therapy
Patients who have received prior treatment with an EGFR or MET inhibitor.
Concurrent Conditions: Patients with symptomatic central nervous system (CNS) metastases who are neurologically unstable or require increasing doses of steroids to control CNS symptoms.
Medical History: Patients with a history of interstitial lung disease or pneumonitis.
Other Malignancies: Patients with another active malignancy within the past 3 years, with the exception of adequately treated basal cell or squamous cell skin cancer or carcinoma in situ.
Pregnancy: Pregnant or breastfeeding women, due to the potential for congenital abnormalities and the potential of this regimen to harm nursing infants.
Contraindications: Patients with known hypersensitivity to any of the components of amivantamab or similar drug classes.
Compliance: Patients who are unable or unwilling to comply with the study protocol.
3 Removal Criteria
Patients may be removed from the study for the following reasons:
3. 1. Disease Progression
As evidenced by clinical or radiographic criteria.
Toxicity: Development of unacceptable toxicity as defined by the protocol.
Non-Compliance: Non-adherence to study treatment or protocol requirements.
Withdrawal of Consent: At any time that the patient withdraws consent.
Investigator Discretion: At the discretion of the investigator for reasons including but not limited to safety concerns or protocol violations.
4 Replacement of Participants
Participants who are removed from the study for reasons other than disease progression may be replaced to ensure that the study meets its intended sample size of 100 patients. This will be done to maintain the statistical power necessary to detect a clinically meaningful difference in the primary endpoint of ORR.
Procedures
Procedures
1 Screening Procedures
1.1 Informed Consent
• Obtain written informed consent from all potential study participants before performing any study-specific procedures.
1.2 Eligibility Assessment
• Confirm eligibility through clinical history, physical examination, and review of medical records.
• Perform laboratory tests to assess organ function and ensure compliance with

inclusion criteria.
• Conduct molecular assays to document EGFR and MET pathway alterations.
2 Enrollment
2.1 Registration
• Register eligible participants into the study.
• Assign unique participant identification numbers.
3 Treatment Administration
3.1 Initial Dosing
• Administer the recommended Phase 2 dose of intravenous amivantamab on Day 1 of each 21-day cycle.
3.2 Dose Adjustments
• Adjust doses based on patient tolerance, according to predefined criteria.
3.3 Concomitant Medications
• Document all concomitant medications taken by participants throughout the study.
4 Monitoring and Assessments
4.1 Efficacy Assessments
• Perform tumor assessments using RECIST v1.1 criteria at baseline and at specified intervals to evaluate response.
4.2 Safety Assessments
• Monitor and record all adverse events.
• Conduct regular physical examinations, vital sign measurements, and laboratory tests.
4.3 Protocol Compliance
• Ensure adherence to the treatment plan and study procedures.
5 Study Duration and Follow-up
5.1 Treatment Period
• Continue treatment until disease progression, unacceptable toxicity, withdrawal of consent, or other discontinuation criteria are met.
5.2 Follow-up Visits
• Schedule follow-up visits for ongoing assessment of treatment response and safety after the end of treatment.
6 Discontinuation of Treatment
6.1 Criteria for Discontinuation
• Discontinue treatment based on disease progression, unacceptable toxicity, patient decision, or investigator judgment.
6.2 Post-Treatment Follow-up
• Conduct a post-treatment follow-up visit to assess late-occurring toxicities and disease status.
7 Data Collection and Management
7.1 Data Recording
• Record all data in case report forms (CRFs) or electronic data capture systems.
7.2 Data Verification
• Perform source data verification to ensure data accuracy and protocol compliance.

8 Study Completion
8.1 Final Assessments
• Complete all final assessments as per the study protocol.
8.2 Study Closure
• Close the study once all participants have completed the study or the study is terminated.
9 Statistical Analysis
9.1 Data Analysis
• Analyze data according to the statistical plan to assess primary and secondary endpoints.
9.2 Reporting of Results
• Prepare and submit results for publication in a peer-reviewed journal.
Statistical Analysis
Statistical Analysis
1 General Considerations
Statistical analyses will be performed using the latest version of a statistical software package deemed appropriate by the study statisticians. The level of significance for all statistical tests will be set at alpha = 0.05, two-sided. All analyses will be based on the intention-to-treat (ITT) population, which includes all enrolled patients who received at least one dose of amivantamab.
2 Sample Size Determination
The sample size of 100 patients was calculated to provide sufficient power to detect a clinically meaningful difference in the primary endpoint of objective response rate (ORR). This calculation assumes an ORR of interest that is significantly greater than the historical control rates for standard therapy in this patient population. Power calculations were based on a one-sample binomial test with a one-sided alpha level of 0.05.
3 Analysis of Primary Endpoint
The primary endpoint, ORR, will be calculated as the proportion of patients achieving a complete response (CR) or partial response (PR) as per RECIST v1.1 criteria. The exact binomial method will be used to compute the 95% confidence interval (CI) for ORR.
4 Analysis of Secondary Endpoints
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. DCR will be calculated as the proportion of patients achieving CR, PR, or stable disease (SD), with its 95% CI estimated using the exact binomial method.
5 Safety Analysis
Safety will be assessed by the incidence and severity of adverse events (AEs), which will be summarized using descriptive statistics. AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE). Serious adverse events (SAEs) and AEs leading to discontinuation will also be summarized.
6 Interim Analysis

An interim analysis may be conducted for safety purposes at a pre-specified point as determined by the study's independent data monitoring committee (IDMC). The IDMC will have predefined stopping rules based on safety data.

7 Data Handling and Record Keeping

Data will be collected and managed using electronic data capture systems. All changes to the data will be tracked through an audit trail. Data will be reviewed and cleaned regularly to ensure accuracy and completeness.

8 Statistical Reporting

Results of the statistical analyses will be reported in accordance with the International Conference on Harmonisation (ICH) E9 guidelines on statistical principles for clinical trials. The final study report will include detailed descriptions of the statistical methods used, along with the results of the primary and secondary analyses.

9 Ethical Considerations

All statistical analyses will be conducted respecting the confidentiality of the trial participants. The study will adhere to the principles of the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines.

10 Amendments to Statistical Analysis Plan

Any amendments to the statistical analysis plan will be documented and justified in a formal amendment to the study protocol. All such amendments will be approved by the study's steering committee and, if required, by the institutional review board (IRB) or ethics committee (EC) before implementation.

Safety

Safety

1 Safety Monitoring

Safety monitoring will be a continuous process throughout the study, with the collection and assessment of adverse events (AEs) and serious adverse events (SAEs). All AEs will be recorded with their onset date, duration, severity, relationship to the study drug, actions taken, and outcomes. AEs will be graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

2 Reporting of Adverse Events

All AEs, regardless of severity or causality, will be reported to the study investigators. SAEs will be reported immediately to the sponsor and regulatory authorities as per regulatory requirements. The study's independent data monitoring committee (IDMC) will review safety data at regular intervals.

3 Management of Adverse Events

The study protocol includes detailed guidelines for the management of specific AEs associated with amivantamab. Dose modifications, including dose reductions, interruptions, or discontinuations, will be implemented based on the severity of AEs.

4 Safety Endpoints

The safety endpoints of the study include the incidence, nature, and severity of AEs and SAEs. Laboratory abnormalities, vital signs, and physical examination findings will also be monitored as part of safety assessments.

5 Interim Safety Analysis
An interim safety analysis may be conducted at a pre-specified point in the study to evaluate the risk-benefit ratio of the treatment. The IDMC will review the interim safety data and may recommend modifications to the study, including early termination, if necessary.
6 Data Safety Monitoring Board (DSMB)
A DSMB will be established to provide independent oversight of the safety aspects of the study. The DSMB will have the authority to recommend continuation, modification, or termination of the study based on periodic reviews of the accumulated safety data.
7 Patient Safety and Well-being
The safety and well-being of patients will take precedence over the scientific goals of the study. Investigators will ensure that patients are informed about the potential risks and AEs associated with amivantamab and will provide appropriate medical care for any AEs that occur.
8 Safety Training
All study personnel will receive training on the safety profile of amivantamab, AE reporting requirements, and the management of AEs. Regular refresher training sessions will be conducted to ensure compliance with safety protocols.
9 Safety Data Collection and Documentation
Safety data will be collected systematically using case report forms (CRFs) or electronic data capture systems. All documentation will be subject to source data verification to ensure the accuracy and completeness of the safety data.
10 Study Discontinuation Due to Safety Concerns
The study may be discontinued at any time if safety concerns arise that warrant cessation of the trial. Such a decision will be made in consultation with the DSMB, regulatory authorities, and the sponsor.
11 Communication of Safety Information
Investigators will communicate new safety information to patients, regulatory authorities, and the scientific community in a timely manner. Any changes to the study protocol or informed consent documents resulting from new safety information will be implemented after approval by the institutional review board (IRB) or ethics committee (EC).
12 Ethical Considerations
The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. Patient safety will always be the primary concern in all aspects of the study.