Study Protocol

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# Background

*Colorectal cancer*is a significant public health concern, ranking as one of the leading causes of cancer-related mortality worldwide. Despite advances in early detection and treatment, the prognosis for patients with advanced or metastatic colorectal cancer remains poor. This is particularly true for those with alterations in the epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition (MET) pathways, which are associated with aggressive tumor behavior and resistance to conventional therapies. The limited efficacy of existing treatment options for this subgroup underscores the urgent need for novel therapeutic strategies.

Amivantamab is a bispecific antibody designed to target both EGFR and MET receptors, thereby disrupting key oncogenic signaling pathways involved in tumor growth and survival. By simultaneously inhibiting these pathways, amivantamab offers a promising approach to overcoming resistance mechanisms that often limit the effectiveness of monotherapy targeting either pathway alone. The dual targeting mechanism of amivantamab has been shown to enhance antitumor activity in preclinical models, providing a strong rationale for its investigation in clinical settings.

Phase 1 clinical trials of amivantamab have primarily focused on patients with non-small cell lung cancer (NSCLC), where the drug has demonstrated a manageable safety profile. The most common adverse events reported were infusion-related reactions, skin rash, and paronychia, which were generally mild to moderate in severity. Importantly, these studies have provided preliminary evidence of clinical efficacy, with notable objective response rates observed in patients harboring EGFR and MET alterations. These findings support the further evaluation of amivantamab in other malignancies characterized by similar molecular aberrations, such as colorectal cancer.

Preliminary efficacy signals from the Phase 1 trials, including tumor shrinkage and prolonged disease stabilization, suggest that amivantamab may offer therapeutic benefit to patients with advanced colorectal cancer who have exhausted standard treatment options. However, comprehensive data on its efficacy and safety in this specific patient population remain limited. This Phase 2 study aims to address this gap by systematically assessing the objective response rate, progression-free survival, overall survival, and disease control rate in patients with EGFR and MET alterations.

In conclusion, the development of amivantamab represents a promising advancement in the treatment landscape for advanced colorectal cancer, particularly for patients with EGFR and MET pathway alterations. The current study seeks to build upon the encouraging results observed in earlier trials, with the potential to establish amivantamab as a new standard of care for this challenging patient population. [RECOMMENDED:*Inclusion of additional biomarkers for patient stratification and response prediction could enhance the study's impact.*]

# Objectives

Phase 2 Study Objectives

*Primary Objective: Efficacy Endpoints*

The primary objective of this Phase 2 study is to assess the efficacy of amivantamab in patients with advanced colorectal cancer exhibiting EGFR and MET alterations. The primary efficacy endpoint is the objective response rate (ORR), which is defined as the proportion of patients achieving a complete or partial response to treatment, as per RECIST 1.1 criteria. This will provide a direct measure of the antitumor activity of amivantamab in this patient population.

*Secondary Objective: Safety Continuation*

The secondary objectives focus on the continued evaluation of the safety profile of amivantamab in the study cohort. This includes monitoring and documenting the incidence, severity, and relationship of adverse events (AEs) to the study drug. Additionally, secondary efficacy endpoints such as progression-free survival (PFS), overall survival (OS), and disease control rate (DCR) will be assessed. These endpoints will provide further insight into the therapeutic benefit and safety of amivantamab.

*Exploratory Objective: Biomarkers*

The exploratory objectives aim to identify and evaluate potential biomarkers that may predict response to amivantamab treatment or provide insights into the mechanisms of resistance. Biomarker analyses will include, but are not limited to, genomic, transcriptomic, and proteomic profiling of tumor samples. This will facilitate the identification of predictive biomarkers and enhance the understanding of the biological underpinnings of treatment response and resistance.

[PLACEHOLDER:*Specify any additional exploratory objectives or endpoints if applicable.*]

[RECOMMENDED:*Consider including an assessment of patient-reported outcomes (PROs) to evaluate the impact of treatment on quality of life.*]

# Study Design

Phase 2 Study Design

*Patient Population*

The study population consists of adult patients aged 18 years or older with advanced or metastatic colorectal cancer characterized by documented alterations in the epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition (MET) pathways. Patients must have experienced disease progression on or after standard therapy, or have no available standard treatment options, to be eligible for inclusion in this study.

*Randomization Strategy*

This study is designed as a single-arm, open-label trial; therefore, randomization is not applicable. All enrolled patients will receive the investigational treatment, amivantamab. [RECOMMENDED: Consideration of a randomized controlled design in future studies to compare amivantamab with standard of care or placebo.]

*Control Group Rationale*

Given the exploratory nature of this Phase 2 study and the focus on assessing the efficacy and safety of amivantamab in a specific patient population with limited treatment options, a control group is not included. The absence of a control group is justified by the need to gather preliminary data on the therapeutic potential of amivantamab in this setting. [RECOMMENDED: Future studies may incorporate a control group to strengthen the evidence base.]

*Dose Selection Justification*

The dose of amivantamab administered in this study is based on the recommended Phase 2 dose established in prior clinical trials, particularly those conducted in non-small cell lung cancer (NSCLC) patients. This dosing regimen is selected to optimize the balance between efficacy and safety, with adjustments permitted based on individual patient tolerance. [PLACEHOLDER:*Specific dose details from prior studies*]

Study Schema Diagram

```mermaid

graph TD

A[Screening] --> B[Randomization]

B --> C[Treatment Phase]

C --> D[Follow-up]

subgraph "Phase 2 Study Flow"

A

B

C

D

end

```

This study schema illustrates the flow of participants through the various stages of the trial, from initial screening to follow-up after treatment.

# Population

*Population*

*Target Patient Population*

The target patient population for this Phase 2 study consists of adults diagnosed with advanced or metastatic colorectal cancer characterized by alterations in the epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition (MET) pathways. These patients have either experienced disease progression following standard therapy or have no available standard treatment options.

*Inclusion Criteria*

1. Adults aged 18 years or older.

2. Histologically or cytologically confirmed diagnosis of advanced or metastatic colorectal cancer.

3. Documented alterations in EGFR and MET pathways.

4. Evidence of disease progression on or after standard therapy, or lack of available standard treatment options.

5. Adequate organ function as defined by laboratory parameters [PLACEHOLDER:*specific laboratory criteria*].

6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

*Exclusion Criteria*

1. Prior treatment with amivantamab or other EGFR/MET-targeting agents.

2. Known hypersensitivity to any component of the study drug.

3. Uncontrolled intercurrent illness, including but not limited to active infection, symptomatic congestive heart failure, or unstable angina.

4. Pregnant or breastfeeding women.

5. Participation in another clinical trial with investigational agents within 28 days prior to study entry.

*Sample Size Calculation*

The sample size for this study is calculated to be 100 patients. This number is determined to provide adequate statistical power to detect a clinically meaningful objective response rate (ORR) with a confidence level of [PLACEHOLDER:*confidence level*] and a power of [PLACEHOLDER:*power level*]. Secondary analyses will focus on progression-free survival (PFS), overall survival (OS), and disease control rate (DCR).

*Recruitment Strategy*

The recruitment strategy will involve collaboration with oncology centers specializing in colorectal cancer treatment. Potential participants will be identified through medical records and cancer registries. Outreach efforts will include informational sessions for healthcare providers and patient advocacy groups to raise awareness about the study. Additionally, digital platforms and social media will be utilized to reach a broader audience. Recruitment materials will be designed to clearly communicate the study's purpose, eligibility criteria, and potential benefits and risks to prospective participants.

[RECOMMENDED: Consider engaging with patient advocacy organizations to enhance recruitment efforts and ensure diverse patient representation.]

# Procedures

*Study Procedures*

Screening Assessments

During the screening phase, which occurs from Day -28 to Day -1, the following assessments will be conducted to determine patient eligibility:

- Obtain*informed consent*from all participants.

- Collect*medical history*and perform a*physical examination*.

- Conduct*laboratory tests*including blood and urine analyses.

- Perform*imaging studies*such as CT or MRI scans to evaluate disease status.

- Obtain a*biopsy*to confirm EGFR and MET alterations.

- Conduct an*ECG*to assess cardiac function.

- Evaluate*performance status*using a standardized scale.

Treatment Administration

The treatment phase involves the administration of amivantamab and includes the following procedures:

- On Day 1 (Baseline), conduct a*physical examination*, record*vital signs*, perform*laboratory tests*(blood and urine), conduct an*ECG*, assess*performance status*, and administer the first dose of amivantamab.

- For Treatment Cycle 1, on Days 1, 8, and 15, perform a*physical examination*, record*vital signs*, conduct*laboratory tests*(blood), assess for*adverse events*, and administer amivantamab.

- For Treatment Cycle 2 and subsequent cycles, on Day 1 of each 21-day cycle, repeat the procedures from Treatment Cycle 1.

Safety Monitoring

Safety monitoring will be conducted throughout the study to ensure patient well-being and to identify any adverse events:

- Regular assessment of*adverse events*at each treatment visit.

- Continuous monitoring of*vital signs*and*laboratory test results*.

- Conduct*ECGs*as needed based on clinical judgment.

Efficacy Assessments

Efficacy assessments are designed to evaluate the therapeutic impact of amivantamab:

- Conduct*imaging assessments*(CT/MRI scans) every 6 weeks to assess tumor response.

- Evaluate*objective response rate (ORR)*as the primary endpoint.

- Assess*progression-free survival (PFS)*,*overall survival (OS)*, and*disease control rate (DCR)*as secondary endpoints.

Study Schedule

Below is a detailed study schedule table formatted as an HTML table. It includes visits, timepoints, and procedures for the Phase 2 study of Amivantamab in patients with advanced colorectal cancer.

```html

<table class="study-schedule">

<tr>

<th>Visit</th>

<th>Timepoint</th>

<th>Procedures</th>

</tr>

<tr>

<td>Screening</td>

<td>Day -28 to Day -1</td>

<td>

<ul>

<li>Informed consent</li>

<li>Medical history</li>

<li>Physical examination</li>

<li>Laboratory tests (blood and urine)</li>

<li>Imaging studies (CT/MRI)</li>

<li>Biopsy for EGFR and MET alterations</li>

<li>ECG</li>

<li>Performance status assessment</li>

</ul>

</td>

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<tr>

<td>Baseline</td>

<td>Day 1</td>

<td>

<ul>

<li>Physical examination</li>

<li>Vital signs</li>

<li>Laboratory tests (blood and urine)</li>

<li>ECG</li>

<li>Performance status assessment</li>

<li>Administration of amivantamab</li>

</ul>

</td>

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<tr>

<td>Treatment Cycle 1</td>

<td>Day 1, Day 8, Day 15</td>

<td>

<ul>

<li>Physical examination</li>

<li>Vital signs</li>

<li>Laboratory tests (blood)</li>

<li>Adverse event assessment</li>

<li>Administration of amivantamab</li>

</ul>

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<tr>

<td>Treatment Cycle 2+</td>

<td>Day 1 of each 21-day cycle</td>

<td>

<ul>

<li>Physical examination</li>

<li>Vital signs</li>

<li>Laboratory tests (blood)</li>

<li>Adverse event assessment</li>

<li>Administration of amivantamab</li>

</ul>

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<tr>

<td>Imaging Assessments</td>

<td>Every 6 weeks</td>

<td>

<ul>

<li>CT/MRI scans to assess tumor response</li>

</ul>

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<tr>

<td>End of Treatment</td>

<td>Within 30 days after last dose</td>

<td>

<ul>

<li>Physical examination</li>

<li>Vital signs</li>

<li>Laboratory tests (blood and urine)</li>

<li>ECG</li>

<li>Adverse event assessment</li>

<li>Performance status assessment</li>

</ul>

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<tr>

<td>Follow-up</td>

<td>Every 3 months for 1 year</td>

<td>

<ul>

<li>Survival status</li>

<li>Adverse event assessment</li>

<li>Additional treatments received</li>

</ul>

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</tr>

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This table outlines the schedule for screening, treatment, and follow-up visits, including the specific procedures to be conducted at each timepoint.

# Statistical Analysis

*Statistical Methods*

Primary Efficacy Analysis

The primary efficacy analysis will focus on evaluating the objective response rate (ORR) of amivantamab in patients with advanced colorectal cancer exhibiting EGFR and MET alterations. ORR will be defined as the proportion of patients achieving a complete response (CR) or partial response (PR) as per RECIST 1.1 criteria. The analysis will employ a binomial exact test to estimate the ORR, with a corresponding two-sided 95% confidence interval. The null hypothesis will be that the ORR is equal to or less than a predefined threshold, which represents the minimal clinically meaningful response rate. [PLACEHOLDER:*Specify the predefined threshold for ORR*].

Secondary Analyses

Secondary analyses will include the evaluation of progression-free survival (PFS), overall survival (OS), disease control rate (DCR), and the safety profile of amivantamab. PFS and OS will be analyzed using Kaplan-Meier survival curves, with median survival times and 95% confidence intervals reported. The log-rank test will be used to compare survival distributions if applicable. DCR will be calculated as the proportion of patients achieving CR, PR, or stable disease (SD) for a minimum duration of 12 weeks. Safety analyses will involve descriptive statistics summarizing the incidence and severity of adverse events, graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version [PLACEHOLDER:*Specify version*].

Interim Analyses

Interim analyses will be conducted to assess safety and efficacy data at predefined time points during the study. These analyses will be guided by a Data Monitoring Committee (DMC) to ensure patient safety and study integrity. The timing and criteria for interim analyses will be determined based on enrollment rates and emerging data. [PLACEHOLDER:*Specify the timing and criteria for interim analyses*]. A stopping rule for futility or overwhelming efficacy will be established, using a pre-specified statistical boundary such as the O'Brien-Fleming or Pocock boundary. [RECOMMENDED:*Consider specifying the statistical boundary method*].

Power Calculations

The sample size of 100 patients is calculated to provide adequate power to detect a clinically meaningful ORR. Power calculations are based on the assumption of a [PLACEHOLDER:*Specify expected ORR*] under the alternative hypothesis, with a significance level (alpha) of 0.05. The study is powered at [PLACEHOLDER:*Specify power level, e.g., 80% or 90%*] to detect this difference. The calculations account for potential dropouts and non-evaluable patients. [RECOMMENDED:*Include sensitivity analyses to assess the impact of varying assumptions on power*].

These statistical methods are designed to rigorously evaluate the efficacy and safety of amivantamab in this patient population, ensuring robust and reliable study outcomes.

# Safety

Safety Monitoring Plan

*Adverse Event Reporting*

Adverse events (AEs) will be systematically collected and reported throughout the study to ensure patient safety and the integrity of the data. All AEs will be documented from the time of informed consent until 30 days after the last dose of amivantamab. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version [PLACEHOLDER:*version number*]. Serious adverse events (SAEs) will be reported to the sponsor and relevant regulatory authorities within 24 hours of the investigator's awareness. Regular safety reports will be compiled and submitted to the Institutional Review Board (IRB) and Data Monitoring Committee (DMC).

*Safety Parameters*

Safety parameters will include, but are not limited to, hematological assessments, biochemical tests, and vital signs. Specific parameters will be monitored at baseline and at regular intervals throughout the study, including:

- Complete blood count (CBC) with differential

- Liver function tests (LFTs)

- Renal function tests

- Electrolyte levels

- Cardiac monitoring, including electrocardiograms (ECGs)

- Physical examinations

*Risk Management*

A comprehensive risk management plan will be implemented to mitigate potential risks associated with amivantamab administration. This plan will include:

- Pre-treatment screening to identify patients at increased risk of adverse reactions

- Close monitoring for infusion-related reactions, with premedication protocols as necessary

- Dose modifications or treatment discontinuation guidelines in response to specific AEs

- Emergency response procedures for severe or life-threatening AEs

*Data Monitoring*

An independent Data Monitoring Committee (DMC) will be established to oversee the safety of study participants and the integrity of the data. The DMC will conduct interim analyses at predefined intervals to evaluate safety data and make recommendations regarding the continuation, modification, or termination of the study. The DMC will consist of experts in oncology, biostatistics, and clinical trial ethics.

[RECOMMENDED:*Consider including a detailed plan for the management of specific AEs commonly associated with EGFR and MET inhibitors, such as skin rash and diarrhea.*]

The safety monitoring plan will be continuously reviewed and updated as new safety information becomes available, ensuring the highest standards of patient care and scientific rigor.

# Endpoints

Study Endpoints

*Primary Efficacy Endpoints:*

The primary efficacy endpoint for this Phase 2 study is the*objective response rate (ORR)*of amivantamab in patients with advanced colorectal cancer exhibiting EGFR and MET alterations. The ORR is defined as the proportion of patients who achieve a complete response (CR) or partial response (PR) as per the Response Evaluation Criteria in Solid Tumors (RECIST) version [PLACEHOLDER:*version number*].

*Secondary Endpoints:*

Secondary endpoints are designed to further evaluate the clinical benefit of amivantamab and include:

1.*Progression-Free Survival (PFS):*The time from the start of treatment until disease progression or death from any cause, whichever occurs first.

2.*Overall Survival (OS):*The time from the start of treatment until death from any cause.

3.*Disease Control Rate (DCR):*The proportion of patients who achieve a complete response, partial response, or stable disease.

4.*Safety Profile:*The incidence, severity, and type of adverse events experienced by patients, assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version [PLACEHOLDER:*version number*].

*Safety Endpoints:*

Safety endpoints will focus on the characterization of the safety profile of amivantamab. This includes:

- The frequency and severity of treatment-emergent adverse events (TEAEs).

- The incidence of serious adverse events (SAEs).

- The occurrence of dose-limiting toxicities (DLTs).

- Laboratory abnormalities and changes in vital signs.

*Exploratory Endpoints:*

Exploratory endpoints are intended to provide insights into potential biomarkers of response and mechanisms of action, including:

-*Biomarker Analysis:*Correlation of EGFR and MET pathway alterations with clinical outcomes.

-*Pharmacokinetics (PK):*Evaluation of the pharmacokinetic profile of amivantamab in the study population.

-*Quality of Life (QoL):*Assessment of patient-reported outcomes using validated QoL instruments such as the [PLACEHOLDER:*instrument name*].

[RECOMMENDED: Consider including additional exploratory endpoints related to genomic or proteomic analyses to further understand the molecular basis of response to amivantamab.]