Background

NSCLC and mesenchymal-epithelial transition (MET) factor
• The majority of lung cancers (85%) are classified as NSCLC.
• Approximately 75% of patients with NSCLC have advanced disease at the time of diagnosis.
• MET is a transmembrane tyrosine kinase receptor activated by hepatocyte growth factor (HGF). MET activation is essential for physiological processes including cell morphogenesis, scattering and migration, proliferation, and protection from apoptosis.
• Aberrant activation of MET via gene amplification or gene mutations, as well as MET protein overexpression, has been reported in NSCLC and other cancer types and can promote tumorigenesis.

Study design
• REGN5093 is a bispecific antibody that binds to MET receptors and prevents HGF binding and causes rapid internalization and degradation of MET.

Exclusion criteria
• MET protein overexpression has been reported in ~25–75% of NSCLC.
• MUTED overexpression has been reported in ~2–5% of NSCLC.
• Patients with NSCLC who have participated in a study of an anticancer therapy, including an approved investigational drug, within 14 days of the first dose of REGN5093.
• Patients with NSCLC who have undergone radiotherapy to the tumor within 2 weeks of the first dose of REGN5093.

Inclusion criteria
• Histologically confirmed NSCLC that is at an advanced stage (unresectable or metastatic disease) and for which there is no standard therapy option likely to convey clinical benefit.
• Patients must have exhausted all approved available therapies.
• Available archival tumor tissue.
• Able to provide biopsy during screening for assessment of MET biomarkers.

Early endosome
Late endosome
Cancer cell
HGF
REGN5093
Figure 1. REGN5093 mechanism of action

Methods

Study design
• This is a first-in-human, Phase 1/2, open-label, multicenter study investigating the safety, tolerability, pharmacokinetics (PK), and efficacy of REGN5093 in patients with MET-altered advanced NSCLC (NCT017070766).

Inclusion criteria
• Histologically confirmed NSCLC that is at an advanced stage (unresectable or metastatic disease) and for which there is no standard therapy option likely to convey clinical benefit.
• Patients must have exhausted all approved available therapies.

Assessment
Tumor
Imaging
Figure 2. Study flow diagram.

Dose escalation
• Reversing treatment for a therapeutic study, or has participated in a study of an investigational agent or an investigational device within 4 weeks of first dose of study therapy.
• Prior treatment with an approved systemic therapy within 3 weeks.

Dose expansion cohorts only:
• Prior treatment with MET-targeted biologic therapy.
• Uncontrolled or active primary brain tumor, central nervous system metastases, leukemoid reaction, or severe cord compression.

Inclusion criteria
• Reciprocal sensitively confirmed NSCLC that is at an advanced stage (unresectable or metastatic disease) and for which there is no standard therapy option likely to convey clinical benefit.

Outcome measures
• Study objectives are provided in Table 2.

Dose escalation:
• To assess safety, tolerability, and PK of REGN5093 for maximum tolerated dose and/or definition of the recommended Phase 2 dose of REGN5093 in patients with MET-altered NSCLC.

Secondary objectives
• To assess immunogenicity as measured by anti-drug antibodies (ADA) to REGN5093.
• To assess other measures of preliminary anti-tumor activity.

Dose expansion:
• To assess safety and tolerability of REGN5093 in each expansion cohort.
• To assess REGN5093 PK and concentrations in serum.
• To assess immunogenicity as measured by ADA to REGN5093.
• To evaluate other measures of preliminary anti-tumor activity.

Exploratory objectives
• To evaluate relationships between efficacy of REGN5093 and baseline MET alteration/mutation/amplification or expression.
• To assess pharmacodynamic changes in putative serum or plasma biomarkers.
• To evaluate the impact on clinical activity of tumor mutational spectrum at baseline and post-treatment in tissue and in circulating tumor DNA.

Figure 3. Dose escalation and dose expansion

Table 1. Key inclusion and exclusion criteria

Table 2. Primary, secondary, and exploratory objectives

Figure 3. Dose escalation and dose expansion

For expansion cohort 3, the choice of sample size is selected based on clinical consideration to explore the safety and anti-tumor activity in the patient population.

Statistical hypothesis
• There is no formal statistical hypothesis for the dose escalation phase of the study; analyses will be descriptive and exploratory in nature.

For dose expansion cohorts:
• Null hypothesis (H0): The ORR per RECIST v1.1 is ≤13%.
• Alternative hypothesis (H1): The ORR per RECIST v1.1 is >13%.

Summary

There is an unmet need for patients with MET-altered advanced NSCLC.

REGN5093 is a MET x MET bispecific antibody that binds two distinct epitopes, blocking HGF binding and causing rapid internalization and degradation of MET.

This Phase 1/2 study is designed to assess the safety and tolerability of REGN5093 to establish the recommended Phase 2 dose, and to seek a signal of anti-tumor activity in patients with MET-altered advanced NSCLC who have exhausted all other approved therapies.

This study is ongoing and is actively enrolling patients.

References

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