# A Phase 1/2 Study of REGN5093, a MET x MET Bispecific Antibody, in Patients with MET-Altered Advanced Non-Small Cell Lung Cancer (NSCLC)

Tracey Rowlands,[1] Anita Boyapati,[1] Siyu Li,[2] Christopher Daly,[1] Frank Seebach,[1] Israel Lowy,[1] Petra Rietschel[1]

[1]*Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA;* [2]*Regeneron Pharmaceuticals, Inc., Basking Ridge, NJ, USA*

## Background

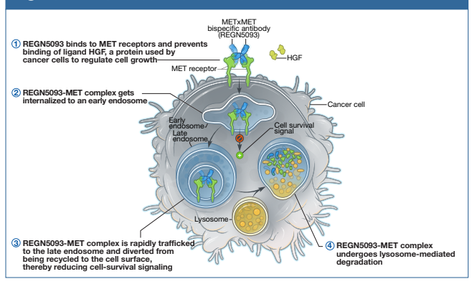
### NSCLC and mesenchymal-epithelial transition (MET) factor

- The majority of lung cancers (85%) are classified as NSCLC.[1,2] Approximately 75% of patients with NSCLC have advanced disease at the time of diagnosis.[3]
- MET is a transmembrane tyrosine kinase receptor activated by hepatocyte growth factor (HGF).[4] MET activation is essential for physiological processes including cell morphogenesis, scattering and motility, proliferation, and protection from apoptosis.[5]
- 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.[6]
  - Mutations in *MET* exon 14 or its flanking introns occur in ~2–4% of NSCLCs.[7,8]
  - *MET* gene amplification has been reported in ~2–5% of NSCLC.[8] As an acquired resistance mechanism to first-line therapy with osimertinib and other epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), *MET* gene amplification has been reported in 7–15% of patients with EGFR mutated NSCLC.[9]
  - MET protein overexpression has been reported in ~25–75% of NSCLC.[8,10]
- In patients with NSCLC, mutations in *MET* exon 14, MET protein expression and increased *MET* copy number have been identified as poor prognostic factors for overall survival (OS).[11,12]
- Selective MET TKIs show efficacy in MET-altered cancers.[12]

### REGN5093

- REGN5093 is a human bispecific antibody that binds to two distinct epitopes of MET, blocking HGF binding and inducing internalization and degradation of MET (**Figure 1**).[13]
- REGN5093 prevents MET-mediated signalling and inhibits growth of MET-driven tumor cells without inducing MET-driven biological responses (**Figure 1**).[13]

**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 (NCT04077099).

- Key inclusion and exclusion criteria are provided in **Table 1**.

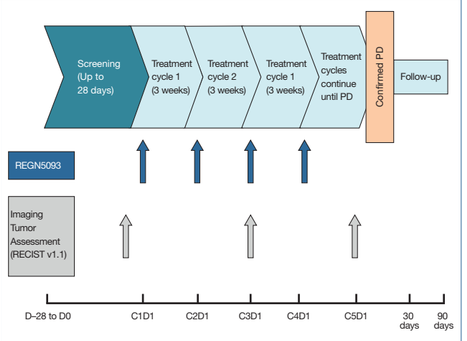
**Table 1.** Key inclusion and exclusion criteria

| Inclusion criteria | Exclusion criteria |
|---|---|
| • Histologically confirmed NSCLC that is at 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 | • Receiving treatment in 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 |
| • Available archival tumor tissue | • Prior treatment with an approved systemic therapy within 3 weeks |
| • Able to provide biopsy during screening for assessment of MET biomarkers | • Dose expansion cohorts only: Prior treatment with MET-targeted biologic therapy |
| • Eastern Cooperative Oncology Group performance status of ≤1 | • Untreated or active primary brain tumor, central nervous system metastases, leptomeningeal disease, or spinal cord compression |
| • Dose expansion cohorts only: At least one lesion measurable by RECIST v1.1[14] | |

RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

- For each patient, the study consists of a screening period of up to 28 days, followed by 3 week cycles of REGN5093 monotherapy (**Figure 2**).
- Study treatment will continue until confirmed disease progression, discontinuation due to intolerable adverse events, or discontinuation per patient and/or investigator decision.
- After a minimum of 24 weeks of treatment, patients with confirmed complete response may elect to discontinue treatment.
- There is a 90-day follow-up period and patients are assessed for survival quarterly after follow-up.
- The study has two parts: dose escalation and dose expansion (**Figure 3**).

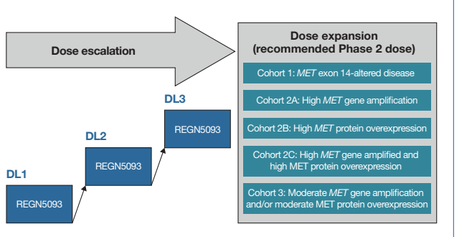
**Figure 2.** Study flow diagram




C, cycle; D, day; PD, progressive disease.

- MET-altered status is determined for eligibility based on patient record only. Central reassessment will be performed retrospectively for all categories of MET alteration.

**Figure 3.** Dose escalation and dose expansion




DL, dose level.

- Dose escalation: Three dose levels of REGN5093 will be investigated as monotherapy. Dose escalation will proceed via a 4+3 design until a maximum-tolerated dose is reached or a recommended Phase 2 dose selected.
- Dose expansion: Once a dose level is selected in the dose escalation part of the study, patients will be allocated to cohorts according to the type(s) of documented biomarkers of MET-altered disease (**Figure 3**).

### Outcome measures

- Study objectives are provided in **Table 2**.

**Table 2.** Primary, secondary, and exploratory objectives

| |
|---|
| **Primary objectives** |
| **Dose escalation**: To assess safety, tolerability, and PK of REGN5093 for determination of the maximum-tolerated dose and/or definition of the recommended Phase 2 dose of REGN5093 in patients with MET-altered NSCLC |
| **Dose expansion**: To determine the ORR per RECIST v1.1 |
| **Secondary objectives** |
| **Dose escalation:**<br>• To determine the ORR per RECIST v1.1<br>• To assess immunogenicity as measured by anti-drug antibodies (ADA) to REGN5093<br>• To evaluate other measures of preliminary anti-tumor activity |
| **Dose expansion:**<br>• To assess safety and tolerability of REGN5093 in each expansion cohort<br>• To assess REGN5093 PK and concentrations in serum<br>• To assess immunogenicity as measured by ADA to REGN5093<br>• To evaluate other measures of preliminary anti-tumor activity |
| **Exploratory objectives** |
| **Dose expansion:**<br>• To evaluate relationships between efficacy of REGN5093 and baseline MET alteration/mutation or amplification/expression<br>• To assess pharmacodynamic changes in putative serum or plasma biomarkers<br>• To evaluate the impact on clinical activity of tumor mutational spectrum at baseline and post-treatment in tissue and in circulating tumor DNA |

DNA, deoxyribonucleic acid; ORR, objective response rate.

### Statistical analysis

#### *Sample size*

- The total number of patients in the study will depend on dose-limiting toxicities documented, resultant cohort sizes, and number of dose levels implemented.
- For expansion cohorts 1, 2A, 2B, and 2C, sample sizes will be based on Simon 2-stage Minimax design with 1-sided significant level of 5% and power of 80%.
- 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 ($H_0$): The ORR per RECIST v1.1 is ≤13%
  - Alternative hypothesis ($H_a$): 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.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For any questions or comments, please contact Tracey Rowlands, Tracey.Rowlands@regeneron.com

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