**Introduction**

Interruption of EGFR signaling, either by blocking EGFR binding sites on the extracellular domain of the receptor or by inhibiting intracellular tyrosine kinase activity, can prevent the growth of EGFR-expressing tumors. EGFR tyrosine kinase inhibitors (TKIs) provide a favorable treatment outcome in EGFR mutation-positive NSCLC patients. However, many patients eventually develop progressive disease after treatment. Such acquired resistance limits the long-term efficacy of these EGFR TKIs in the clinic. The mechanism of acquired resistance include a variety of mutations of the EGFR and crosstalk with the adjacent cMet receptors that allow the tumor to partially compensate the EGFR activity.

**EMB-01** is an innovative bispecific antibody developed based on EpimAb's proprietary FIT-Ig® platform to target EGFR and cMet on tumor cells simultaneously. The anti-EGFR and anti-cMet Fab domains in each EMB-01 arm are fused directly in tandem in a unique crisscross orientation without any mutations or use of peptide linkers to form a final tetravalent binding complex with the corresponding receptors on cell surface. We demonstrated the potential benefit of EMB-01 in treating EGFR and/or cMet driven cancers, particularly in NSCLC-PDX models derived from patients with acquired resistance due to secondary EGFR mutations in the kinase domain or cMet amplification and mutation. Currently, EMB-01 is under evaluation in a Phase I/II clinical trial with advanced/metastatic solid tumors. [ClinicalTrials.gov ID: NCT03797391]

**Characterization of EMB-01 Binding to Cell Surface Antigen**

**EMB-01 Shows Similar Binding to Cell Surface EGFR and cMet Compared to Its Parental mAbs**

- Western blot analysis of antibody induced dimer (true) and EGFR degradation in NCI-H722, NCI-H1975, and H441 cell lines. Cells were left untreated (lane 1) or treated with 1ug/ml of anti-EGFR mAb (lane 2), parental anti-cMet mAb (lane 3), or parental anti-EGFR/anti-cMet mAb (lane 4). Densitometric analysis was performed for total levels of dimer, EGFR (GAPDH loading control).

**Characterization of EMB-01 Binding to Soluble Antigen**

**EMB-01 Maintains Binding Affinities of Parental mAbs**

<table>
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<tr>
<th>EMB-01</th>
<th>Anti-EGFR mAb</th>
<th>Anti-cMet mAb</th>
<th>Human IgG1</th>
<th>Anti-EGFR mAb</th>
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</table>

**Conclusion**

- EMB-01 is a tetrafunctional bispecific antibody targeting EGFR and cMet on the tumor cell.
- EMB-01 was found to induce co-degradation of EGFR and cMet in various tumor cell lines, and such effect is observed by each of the parental mAb alone in combination.
- Highly potent and durable efficacy from EMB-01 binding and biological activity.
- EMB-01 is under evaluation in a Phase I/II clinical trial with advanced/metastatic solid tumors. [ClinicalTrials.gov ID: NCT03797391]

**EMB-01: An innovative bispecific antibody targeting EGFR and cMet on tumor cells mediates a novel mechanism to improve anti-tumor efficacy**

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Reference:
Gong, S., Ren, F., Wu, D., Wu, K., and Wu, C. 2017. Fdbs--a tandem modularisation is a novel and versatile bispecific design for engaging multiple therapeutic targets. mAbs 9, 7, pp.1118–1128