**Abstract**

EGFR is a member of the human epidermal growth factor receptor (ErbB) family with tyrosine kinase activity. Evidence indicates that EGFR is involved in the pathogenesis and progression of human carcinoma of different types. HER3 is a unique pseudokinase receptor of the ErbB family known to mediate resistance to EGFR-targeting therapies. Therefore, we created SI-B001, an EGFR/HER3 bispecific antibody, which can bind EGFR/EGFR homodimers and EGFR/HER3 heterodimers to block their downstream pathways. We performed non-clinical studies to investigate in vitro and in vivo anti-tumor effects.

In vitro, the inhibition of tumor cell growth by SI-B001 was stronger than cetuximab and duligotuzumab in FaDu (mRNA expression levels of EGFR high/HER3/HER3/HER3) cells. Importantly, testing with the cell line Cka-1 (mRNA expression levels of EGFR high/HER3/HER3/NGR1) showed that NGR1 supplementation did not change the potency of cetuximab. However, SI-B001 showed much stronger potency than cetuximab and duligotuzumab under conditions of NGR1 supplementation. This result indicates that the functionality of the bi-specific SI-B001 is competitive against a HER3 natural ligand and capable to act against cancer with HER3 ligand-mediated resistance to cetuximab.

In vivo, single agent SI-B001 exhibited superior anti-tumor activity to cetuximab in the FaDu xenograft model. Meanwhile, SI-B001 in combination with paclitaxel and carboplatin led to a significant synergistic anti-tumor effect, which was stronger than the combination of cetuximab + paclitaxel + carboplatin. Compared to chemotherapy alone in this model, which could result in weight loss and treatment-related mortality, no serious weight loss or deaths occurred in the single agent SI-B001 and the combination of SI-B001 with chemotherapy. These results suggest that SI-B001 alone and in combination with chemotherapy can exhibit favorable safety and robust anti-tumor activity. Currently, 6 phase II clinical trials of SI-B001, either alone or in combination with chemotherapy, have been conducted in different epithelial carcinomas. These studies have shown a potential break-through activity in NSCLC and HNSCC with a very good safety profile.

**Additive efficacy observed with standard of care chemotherapy in EGFR+ xenograft models**

**SI-B001 blocks ligand-induced signaling**

**SI-B001 inhibits EGFR+, HER3+ cell proliferation**

**SI-B001 induces Fc-mediated effector activity**

**Greatest reduction in tumor size observed with SI-B001 treatment combination with chemotherapy**

**Summary**

**In vitro**

- SI-B001 inhibits wild type EGFR signaling pathway
- SI-B001 inhibits NRG-1 induced HER3 signaling pathway
- SI-B001 inhibits NRG-1 mediated growth in the presence of EGFR inhibition

**In vivo**

- SI-B001 in combination with paclitaxel and carboplatin induced a significant synergistic antitumor effect, which was greater than the combination of parental αEGFR + paclitaxel + carboplatin.

**Additive efficacy observed with standard of care chemotherapy in EGFR+ xenograft models**

**SI-B001 combination with Paclitaxel and Carboplatin**

**SI-B001 combination with Cisplatin and Pemetrexed**

**SI-B001 inhibits EGFR+, HER3+ cell proliferation**

**SI-B001 Induces Fc-mediated Effector Activity**

**References**

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