SYSTIMMUNE

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Anti-tumor efficacy of SI-B001, a novel EGFR×HER3 bispecific antibody, against EGFR-driven epithelial tumors alone or in combination with paclitaxel and carboplatin

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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 and 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 heterodimer 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/HER3high/NRG1medium). Importantly, testing with the cell line Oka-c-1 (mRNA expression levels of EGFR high/HER3high/NRG1low), showed that NRG1 supplementation did not change the potency of cetuximab. However, SI-B001 showed much stronger potency than cetuximab and duligotuzumab under conditions of NRG1 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 antitumor 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 combination with Paclitaxel and Carboplatin

SI-B001 combination with Cisplatin and Pemetrexed

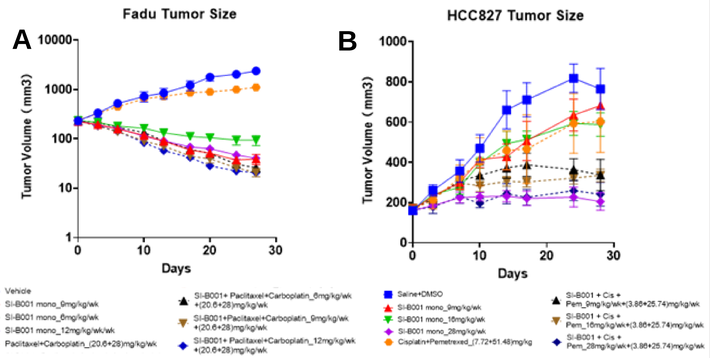
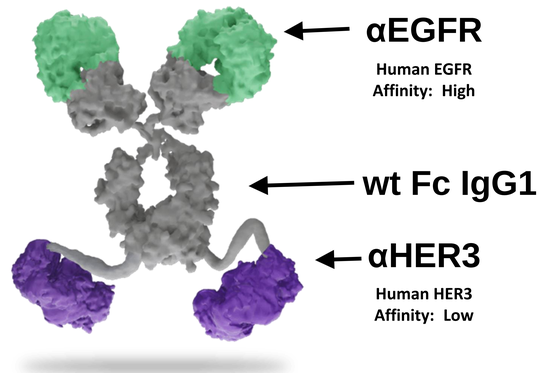


Figure 1. Activity of SI-B001 as a single agent and in combinations with other drugs in tumor xenograft models
The Mean volume over time of tumors detected in each treatment and control group in the subcutaneous xenograft models using (**A**) FaDu NSCLC (n = 8) and (**B**) HCC827 NSCLC (n = 5). Error bars represent SEM.

SI-B001 (Izalontamab): bi-specific EGFR & HER3



SI-B001 blocks ligand-induced signaling

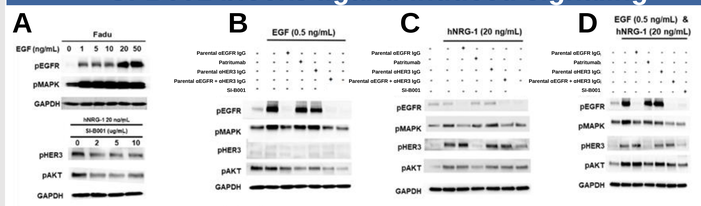


Figure 2. Impact of SI-B001 on cancer cell signaling
(**A**) Dose-dependent ligand-mediated signaling through EGFR and MAPK in FaDu H&N cancer cells. SI-B001-mediated inhibition of NRG1 signaling through HER3 and Akt in FaDu cells. Anti-EGFR, anti-HER3, antibody combination, and SI-B001-mediated inhibition of signaling initiated by EGF (**B**), NRG1 (**C**), and EGFR and NRG1 (**D**) in FaDu H&N cancer cells. Western blotting to detect pEGFR, pMAPK, pHER3, and pAkt with GAPDH protein as a loading control

SI-B001 inhibits EGFR+, HER3+ cell proliferation

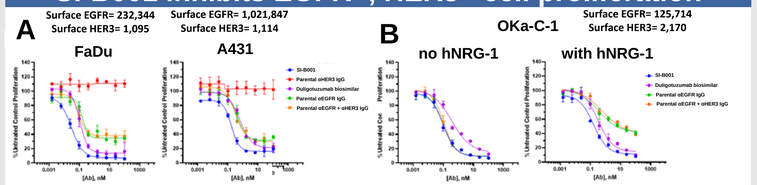


Figure 3. Impact of SI-B001 on cancer cell proliferation
Anti-EGFR, anti-HER3, antibody combination, and SI-B001-mediated inhibition of FaDu and A431 cell proliferation (**A**). Anti-EGFR, anti-HER3, antibody combination, and SI-B001-mediated inhibition of OKa-C-1 cell proliferation in the absence (left) and the presence (right) of hNRG-1 (**B**).

SI-B001 Induces Fc-mediated Effector Activity

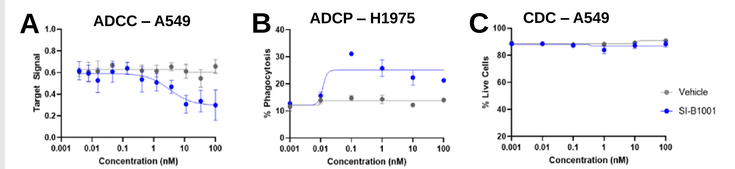


Figure 4. Impact of SI-B001 on antibody Fc-mediated effector functions
ADCC as detected in cells following 36-hour incubation with SI-B001 in the presence of NK cells at 10:1 E:T ratio with 40 IU IL-2/mLH (**A**). ADCP was detected in PHK26-labelled NCI-H1945 cells following a one-hour incubation with SI-B001 in the presence of primary monocyte-derived macrophages at 5:1 E:T ratio (**B**). CDC was measured in A549 cells following a two-hour incubation with SI-B001 in the presence of 40% normal human complement serum (**C**).

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

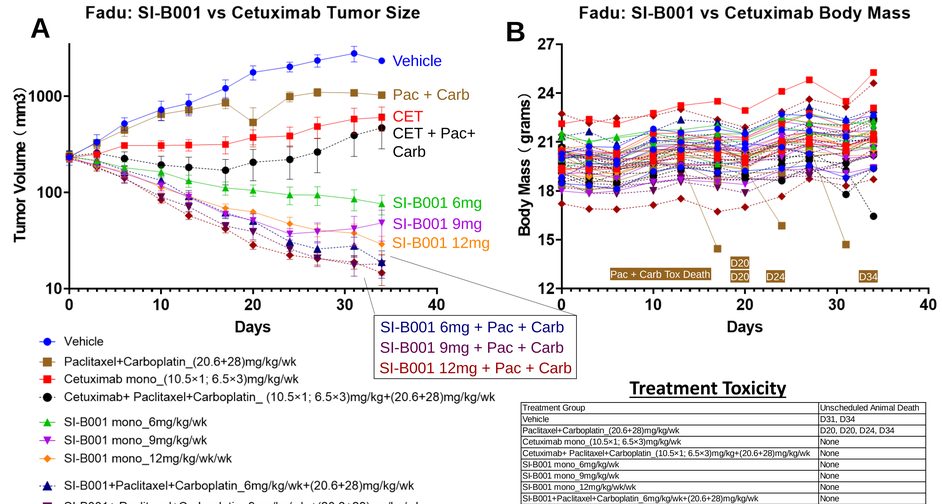


Figure 5. Activity of SI-B001 as a single agent and in combinations with other drugs in tumor xenograft models
The mean tumor volume (**A**) and body mass (**B**) over time detected in each treatment and control group in subcutaneous FaDu H&N xenograft (n=5). Error bars represent standard error of the mean (SEM).

Treatment Toxicity

Treatment Group	Unscheduled Animal Death
Vehicle	D31, D34
Paclitaxel+Carboplatin_(20.6+28)mg/kg/wk	D20, D20, D24, D34
Cetuximab mono_(10.5×1; 6.5×3)mg/kg/wk	None
Cetuximab+ Paclitaxel+Carboplatin_(10.5×1; 6.5×3)mg/kg+(20.6+28)mg/kg/wk	None
SI-B001 mono_6mg/kg/wk	None
SI-B001 mono_9mg/kg/wk	None
SI-B001 mono_12mg/kg/wk/wk	None
SI-B001+Paclitaxel+Carboplatin_6mg/kg/wk+(20.6+28)mg/kg/wk	None
SI-B001+ Paclitaxel+Carboplatin_9mg/kg/wk +(20.6+28)mg/kg/wk	None
SI-B001+ Paclitaxel+Carboplatin_12mg/kg/wk+(20.6+28)mg/kg/wk	None

- ***In vivo*, SI-B001 exhibited superior anti-tumor activity to parental αEGFR in the FaDu xenograft model.**
- **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.**

Summary

In vitro mechanism of action

- 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 combination feasibility

- SI-B001 combination with Paclitaxel and Carboplatin shows additive benefit
- SI-B001 combination with Cisplatin and Pemetrexed shows additive benefit

In vivo combination comparison

- SI-B001 combination with chemo is significantly more efficacious than Cetuximab combination with chemo

Acknowledgments

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SI-B001 clinical trials:

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