Targeted Immunotherapy with Anti-HVEM mAb: A New Hope for Solid Tumors

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BACKGROUND

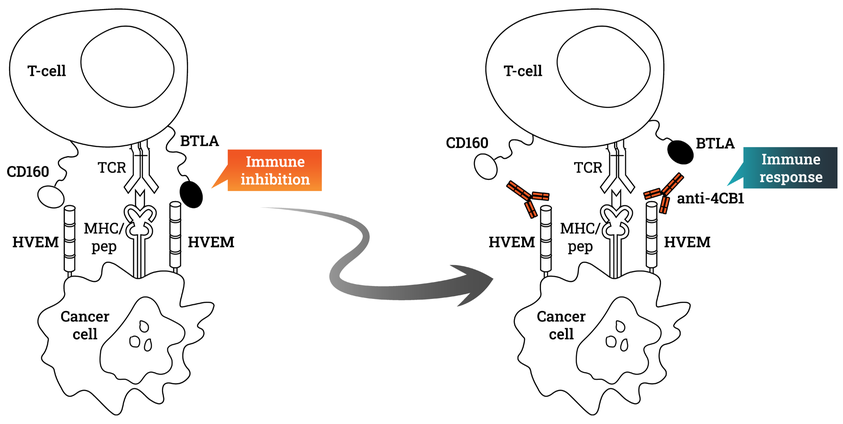
- Immune modulating agents mark a major advancement in cancer therapy
- Despite the success of CTLA4 and PD1/PD-L1 pathway-targeting drugs, many patients fail to respond or develop resistance
- **New anti-tumor agents are urgently needed**
- We have established a **patient-derived** platform for the discovery of novel targets in the field of Immuno-Oncology, which highlighted HVEM, a TNF receptor, as a promising potential target for immunotherapy
- HVEM binding to BTLA or CD160 results in inhibition of T-cell activation, making it a critical regulator of immunity

METHODS

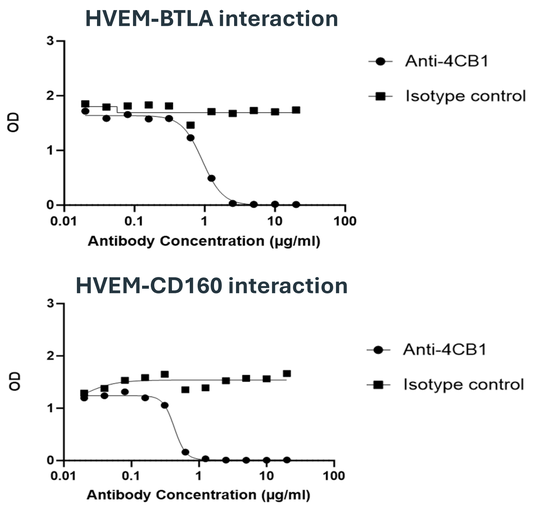
- Anti-4CB1, a fully human mAb, was developed by phase display
- MOA was assessed by ELISA and cell-based co-inhibitory reporter assay
- Anti-tumor activity of Anti-4CB1 was evaluated in-vitro, ex-vivo, and in-vivo, alone and in combination with Anti-PD1
- Sera HVEM levels were assessed by ELISA to correlate with response in ex-vivo experiments using samples from cancer patients
- Safety of Anti-4CB1 was assessed in a Cytokine Release Assay in whole blood, in a specificity assay and in a repeated dose GLP toxicity study in Cynomolgus monkeys

RESULTS

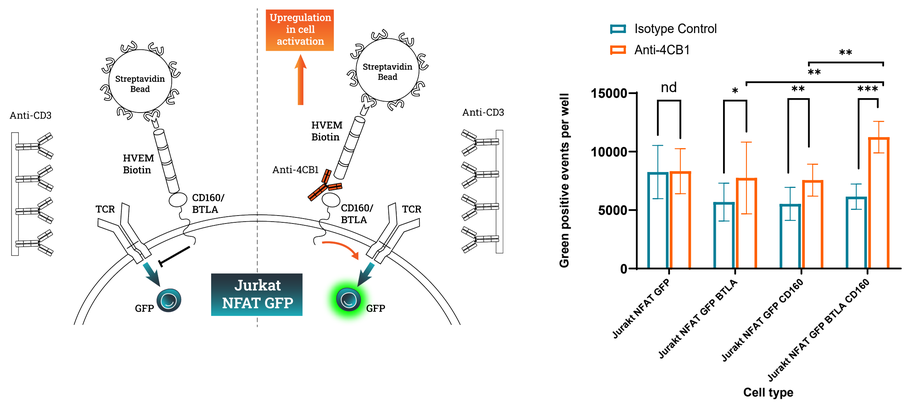
Mechanism Of Action



BLOCKING LIGAND INTERACTIONS



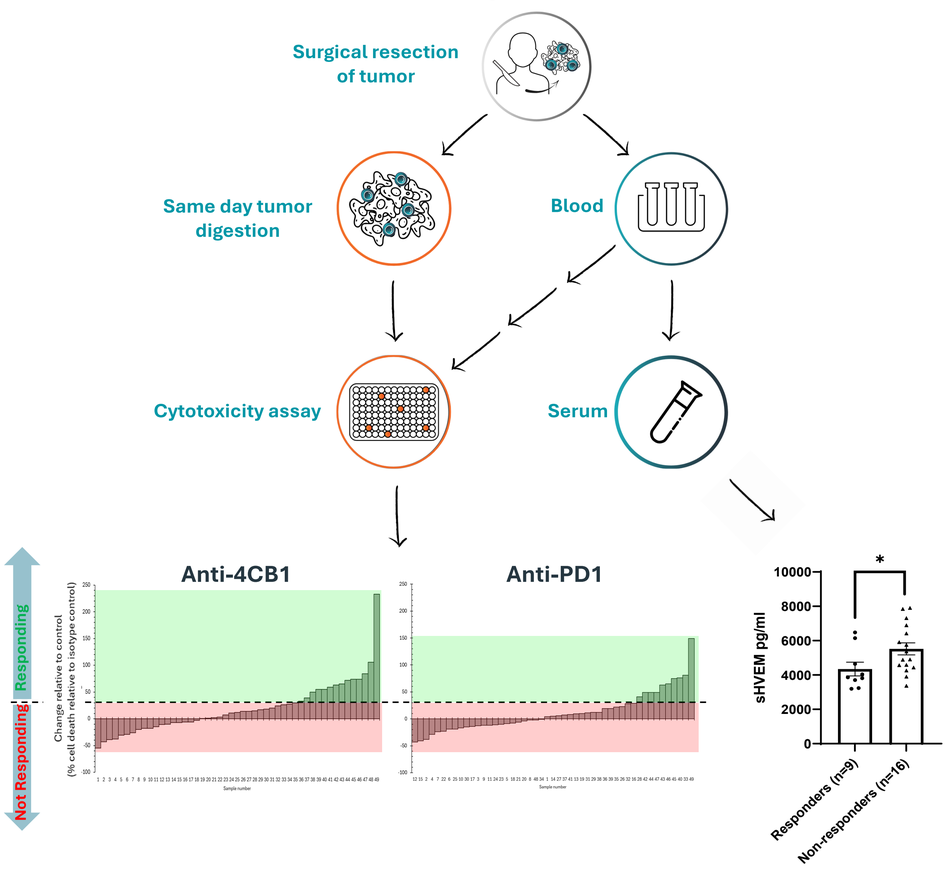
CO-INHIBITORY REPORTER ASSAY



Efficacy

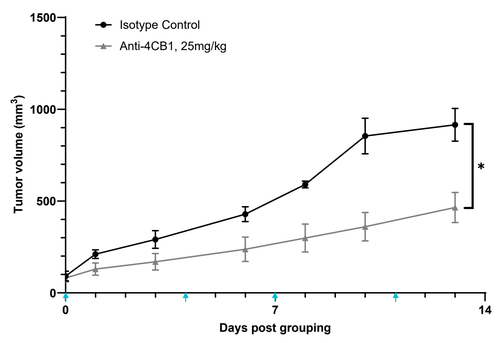
EX-VIVO CYTOTOXICITY

Cytotoxicity assay using cancer clinical samples and autologous PBMCs

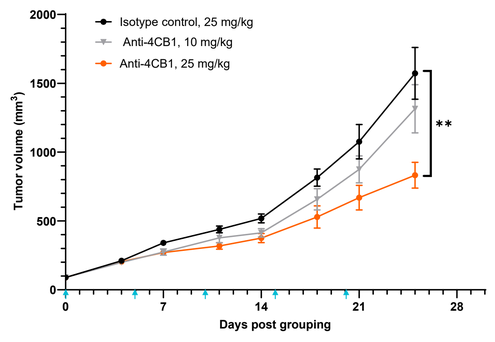


IN-VIVO MONOTHERAPY

Humanized model: Myeloid boosted humanized NCG mice inoculated with melanoma PDX

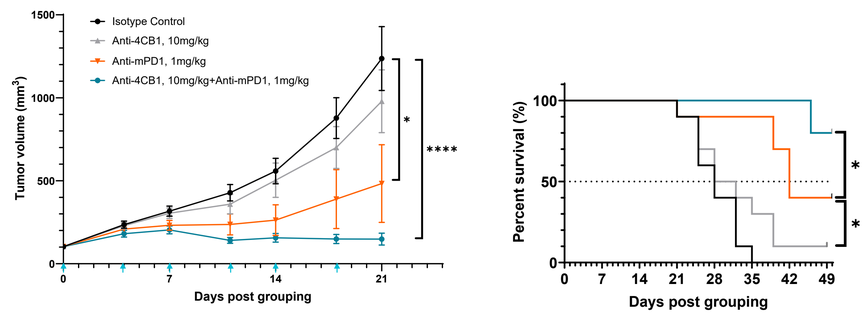


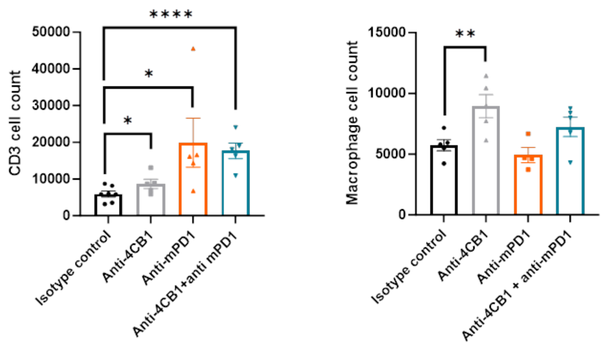
Transgenic model: C57BL/6 expressing hBTLA/hHVEM inoculated with MC38 colon cancer expressing hHVEM



IN-VIVO COMBINATION THERAPY

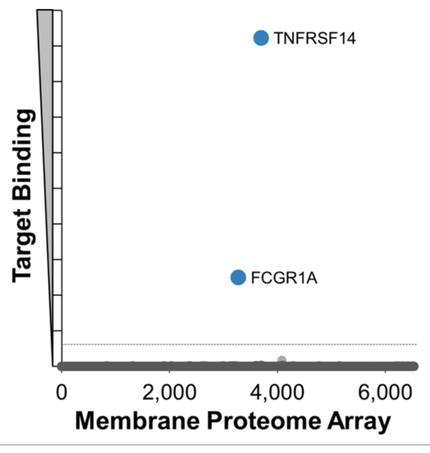
Transgenic model: C57BL/6 expressing hBTLA inoculated with MC38 colon cancer expressing hHVEM





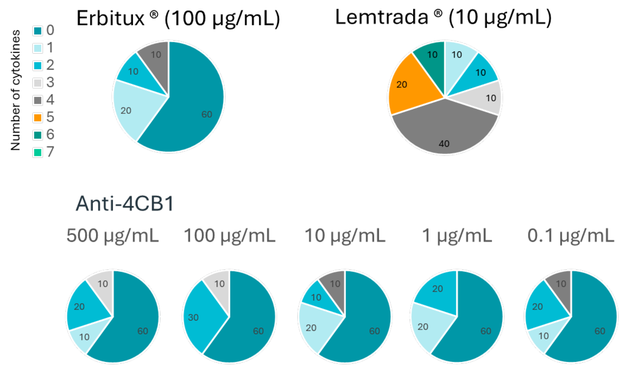
Safety

SPECIFICITY



CYTOKINE RELEASE

Frequency (%) of donors showing multiple cytokine responses



REPEATED DOSE GLP TOXICITY STUDY

Study Groups

- Control vehicle
- Low dose (25 mg/kg)
- Intermediate dose (75 mg/kg)
- High dose (225 mg/kg)

Study Design

- Dosing (Days 1, 16 and 29)
- Scheduled sacrifice (Day 30 of dosing phase, Day 43 of recovery phase)

Three IV administrations of 25, 75 or 225 mg/kg of Anti-4CB1 to cynomolgus monkey were well tolerated

CONCLUSIONS

Specific binding and blocking **No Off-Targets**	**X2 More Effective Ex-Vivo** Anti-4CB1 is effective in twice as many patient samples as Anti-PD1	**As Monotherapy** Up to **53%** Tumor Growth Inhibition In-Vivo	Soluble HVEM is a potential predictive **Biomarker**	**In Combination With Gold Standard** **96%** Tumor Growth Inhibition In-Vivo **20%** Total eradication **X2** Increase in survival	**Safe profile in-vitro and in-vivo** **225 mg/kg** NOAEL

Acknowledgments:

References:

1. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. Science 2018;359(6382):1350-5
2. Rodriguez-Barbosa JI, Schneider P, Weigert A, et al. HVEM, a cosignaling molecular switch, and its interactions with BTLA, CD160 and LIGHT. Cell Mol Immunol 2019;16(7):679-82

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