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BH3120: A Novel Bispecific Antibody Targeting 4-1BB and PD-L1 with Well Balanced Efficacy and Safety Profiles

Jiangcheng Xu, Yang Liu, Jing Wang, Fei Fan, Haitao Gu, Lanxin Zhang, Jun Wang, Ding Song, Ailong Guo, Hongjuan Zhang, Kaixuan Su, Jiaojiao Su, Lijuan Li, Jingmei Cai, Aihong Zhang, Jiawang Liu, Kyoungwoo Lee
Beijing Hanmi Research Center, Beijing Hanmi Pharmaceutical Co., Ltd., the People's Republic of China

ABSTRACT

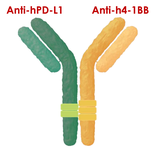
4-1BB (CD137, TNFRSF9) is a promising co-stimulatory signaling mediator of T cells and NK cells, and agonistic monoclonal antibodies targeting 4-1BB are under investigation with aim to observe sufficient and prolonged anti-tumor efficacy. These trials, however, have resulted in limited efficacy or safety, and different bispecific approaches are being explored to overcome these limitations.

BH3120, a bivalent bispecific antibody generated by Pentambody® platform targeting 4-1BB and PD-L1 simultaneously, demonstrates strong and prolonged anti-tumor efficacy as monotherapy, and favorable safety profiles up to dose level of 200 mg/kg in non-human primates. Moreover, combination of BH3120 with an immune checkpoint inhibitor shows significantly synergistic anti-tumor efficacy.

Supported by these data, BH3120 is under IND enabling stages, planning for clinical studies later in 2022.

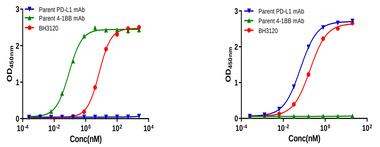
Characteristics

Development Rationale & Goal



- Our goal is to develop a novel bivalent 4-1BB/PD-L1 bispecific antibody using Pentambody® platform, with balanced potency and safety profiles.
- Simultaneously targeting both the inhibitory signaling (PD-L1 blockade) and co-stimulatory signaling (4-1BB clustering and agonism) may result in enhanced magnitude and duration of anti-tumor immune responses, compared to each monoclonal antibody.
- BH3120 enable tumor-localized 4-1BB stimulation to activate T cell and NK cell function. BH3120 shows promising anti-tumor efficacy, whereas minimizing undesirable toxicities.

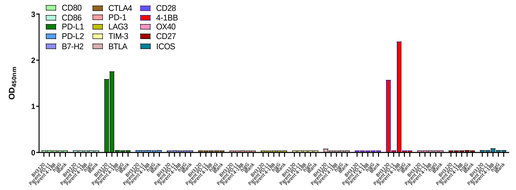
Binding Affinity



Antigen	kon (1/ms)	koff (1/s)	KD (nM)
Human 4-1BB	6.48E+05	7.20E-02	111
Cynomolgus 4-1BB	8.60E+05	2.10E-01	244

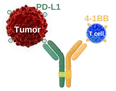
Antigen	kon (1/ms)	koff (1/s)	KD (nM)
Human PD-L1	7.15E+05	3.22E-03	4.50
Cynomolgus PD-L1	1.22E+06	3.47E-03	2.84

Binding Specificity to hPD-L1 and h4-1BB



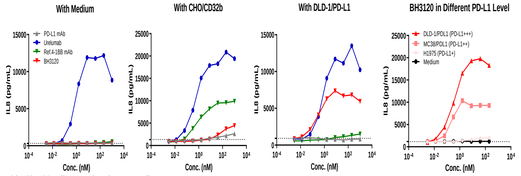
*tested by ELISA and BLI

Mode of Action



- With different binding kinetics against PD-L1 and 4-1BB, BH3120 binds to PD-L1 for relatively longer time inhibiting PD-1/PD-L1 axis, while moderately stimulating 4-1BB receptors on the surface of immune cells.
- BH3120 provides sufficient co-stimulatory signals while reducing the possibility to exhaust T cells and NK cells.

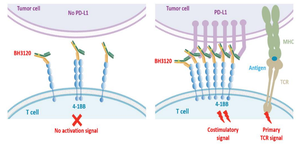
PD-L1 Binding Dependent 4-1BB Agonism

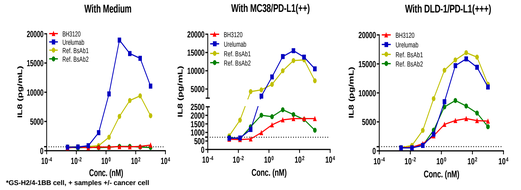


*GS-H2/4-1BB cell, + samples +/- cancer cell

		Urelumab	Ref. 4-1BB mAb	BH3120
Format		IgG4 Monoclonal	IgG4 Monoclonal	IgG1/N297A Bispecific
Epitope Mediated Activation	Relative Binding Affinity to 4-1BB	Strong	Weak	Weaker
	Non-specific T Cell Activation	O	X	X
FcγR Mediated Activation	Binding to FcγR (CD32b)	O	O	X
	FcγR (CD32b) Dependent T Cell Activation	O	O	X
PD-L1 Mediated Activation	Binding to PD-L1	X	X	O
	PD-L1 Dependent T Cell Activation	X	X	O

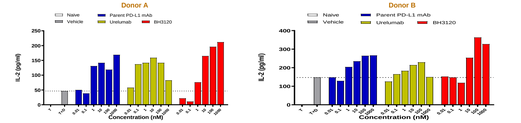
- BH3120 activates immune cells in PD-L1 binding dependent, but not CD32b dependent manner. Immune stimulation activity by BH3120 depends on the expression level of PD-L1 in adjacent cells.
- When compared with reference BsAbs (Ref. BsAb1: high affinity tetravalent, Ref. BsAb2: high affinity bivalent), BH3120 shows moderate immune stimulating activity in vitro without hook effect in broad range of concentration.





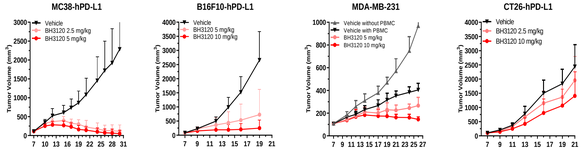
*GS-H2/4-1BB cell, + samples +/- cancer cell

Mixed Lymphocyte Reaction Assay

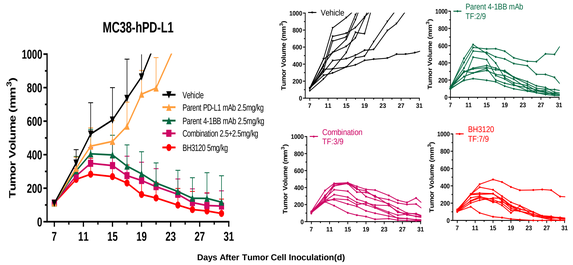


in vivo Anti-tumor Activity

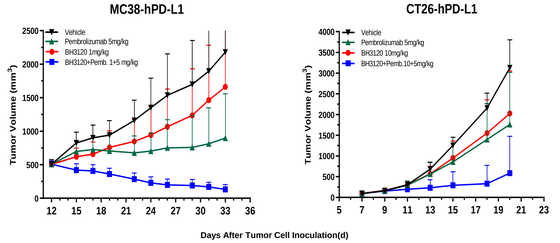
Dose Dependent Efficacy in Different Tumor Models



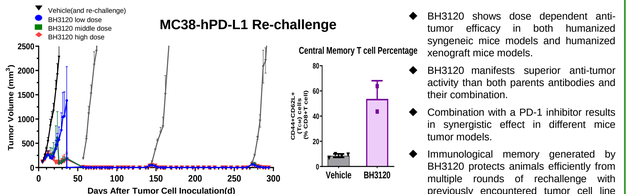
Comparison with Parent Antibodies and Their Combination



Combination with PD-1 Antagonist



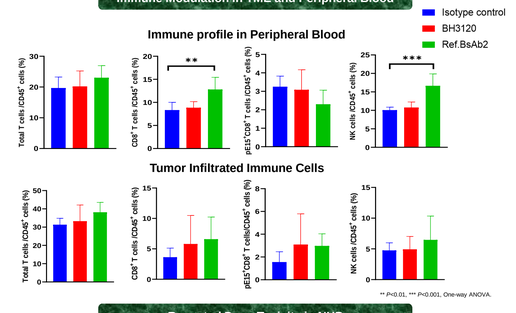
Prolonged Protection by Immune Memory



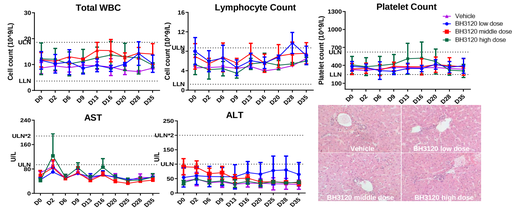
- BH3120 shows dose dependent anti-tumor efficacy in both humanized syngeneic mice models and humanized xenograft mice models.
- BH3120 manifests superior anti-tumor activity than both parents antibodies and their combination.
- Combination with a PD-1 inhibitor results in synergistic effect in different mice tumor models.
- Immunological memory generated by BH3120 protects animals efficiently from multiple rounds of rechallenge with previously encountered tumor cell line until when the observation was finished.

Preclinical Safety

Immune Modulation in TME and Peripheral Blood



Repeated Dose Toxicity in NHP



- BH3120 underwent multiple rounds of safety evaluation in both tumor bearing rodents and naive NHPs at high doses.
- Comparing to a reference bivalent BsAb (Ref.BsAb2) who has high affinity against the targets, modulation of T cell by BH3120 is focused on the sites of tumor burden, while peripheral alteration is minimized suggesting that BH3120 may have decreased risk of off tumor immune boosting that has been observed with some T cell co-stimulatory modulators.
- During repeated dose toxicity studies in NHPs, there were no increase of peripheral lymphocytes and no decrease of neutrophil or platelet in hematology tests. Except for transient elevation of AST following each dosing, no abnormal findings were observed in serum chemistry and liver pathology examinations.

CONCLUSION

- BH3120 is an IgG like bivalent bispecific antibody generated based on Pentambody® platform. It targets 4-1BB and PD-L1 simultaneously with high affinity against human and monkey PD-L1 and moderate affinity against human and monkey 4-1BB. It stimulates 4-1BB conditionally in PD-L1 binding dependent manner without hook effects in potential therapeutic concentration range.
- These properties result in sufficient efficacy in different tumor models in dose dependent ways and the efficacy is maintained for long period of time with increased memory T cells. Combination of low dose BH3120 with a PD-1 antagonistic antibody further enhances anti-tumor efficacy efficiently diminishing enlarged tumor burdens.
- Differently from reference bispecific antibodies with altered valency and affinity ranges, BH3120 modulates immune profile particularly focusing on tumor microenvironment, but not on peripheral blood, suggesting minimal modulation of systemic or non tumor specific immune activity. These characteristics of BH3120 would result in differentiated safety profiles as observed in multiple safety evaluations with rodents and non-human primates. Up to 200 mg/kg in cynomolgus monkeys, BH3120 shows favorable and stable hematological and biochemical parameters.
- Together with additional studies to better understand the mode of action, IND enabling studies are underway to support clinical evaluation of BH3120.

Reference:
1 Segal NH, Logan TF, Hodi FS, et al. Results from an integrated safety analysis of Urelumab, an agonist anti-CD137 monoclonal antibody. Clin Cancer Res. 2017 Apr 15;23(8):1929-1936. doi: 10.1158/1078-0432.CCR-16-1272.
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Beijing Hanmi Pharmaceutical Co., Ltd. (www.bjhanmi.com.cn)

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