Abstract #698

A Phase 1, Open-Label, Multinational, Multicenter, Dose Escalation and Expansion Study of BH3120 (4-1BB x PD-L1 BsAb) in Patients with Advanced or Metastatic Solid Tumors

Dong-Wan Kim[1], Hye Ryun Kim[2], Se-Hoon Lee[3], Se Hyun Kim[4], Jae-Lyun Lee[5], Minal Barve[6], Alexander Starodub[7], John Sarantopoulos[8], Seong-jung Kim[9], Sooa Jung[9], Taewan Kim[9], Jiyeon Yoon[9], Heera Roh[9], Yesong Shin[9], Hyunjin Kim[9], Eunhye Baek[9] and Young Su Noh[9]

[1]Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea, [2]Division of Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea, [3]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, [4]Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul, Korea, [5]Division of Oncology, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, [6]Mary Crowley Cancer Research, Dallas, TX, [7]Christ Hospital Cancer Center, Cincinnati, OH, [8]Institute for Drug Development, Mays Cancer Center at University of Texas Health San Antonio MD Anderson Cancer Center, San Antonio, TX, [9]Department of ONCO Clinical Research and Development, Hanmi Pharmaceutical Co., Ltd., Seoul, Korea

BACKGROUND

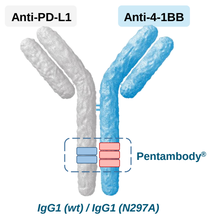


Figure 1. Structure of BH3120

- BH3120 is an IgG like bivalent, bispecific antibody based on Pentambody® platform targeting both 4-1BB and PD-L1.
  - 4-1BB arm function as a 4-1BB agonist to cluster 4-1BB receptors and activate co-stimulatory signals
  - PD-L1 arm function as an anchor for 4-1BB receptors and an antagonist for PD-1/PD-L1 mediated signals
  - BH3120 function as a T-cell engager that bridges T-cells with tumor cells specifically in the micro-environment (TME)
- The concept of immune checkpoint inhibition, including PD-1/PD-L1 antagonist, was proposed as one of the anti-cancer mechanism to manage the tumor burden by modulating tumor specific immune system.
- PD-(L)1 targeting drugs has been proven to be effective but at the same time, showed activity towards limited population and is often associated with systemic and non-tumor specific immune modulation which may lead to multiple adverse reactions[1].
- Limitation of the checkpoint inhibitors led to active investigation of combination therapies with intention to target multiple anti-tumor mechanisms thereby increasing the anti-tumor activity as well as supporting prolonged activity.
- 4-1BB (CD137), a member of the TNF receptor superfamily, is one of the T cell co-stimulatory receptor, and signaling via 4-1BB agonists results in the activation of CD8⁺ T cell[2].
- 4-1BB became promising target for immunotherapy, but with its strong co-stimulatory signal, liver-related toxicities remains as a major hurdle for drug development.
- BH3120 was designed to elaborate past limitations of checkpoint inhibitors as well as focusing on TME specific activation of 4-1BB.

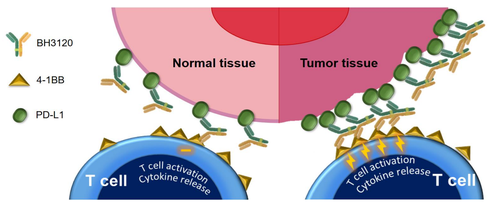


Figure 2. Illustration of decoupling T-cell activation mechanism of BH3120[3]

- BH3120, with its moderate 4-1BB binding affinity, is insufficient to cluster and activate 4-1BB receptors of normal tissue with low PD-L1 expression.
- In PD-L1 positive tumor tissue, BH3120 binds to PD-L1 allowing stable and sufficient clustering of 4-1BB receptors inducing strong and durable cytotoxicity.

PHARMACOLOGICAL ACTIVITY

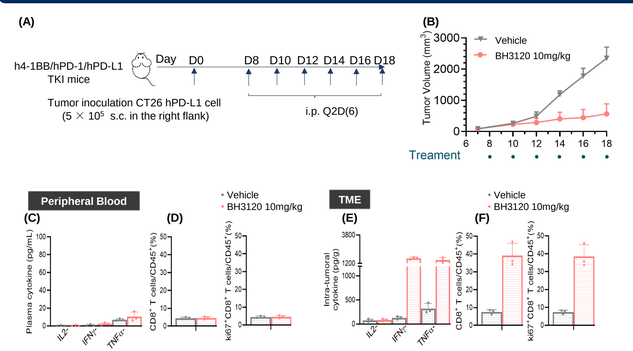


Figure 3. Decoupling of immune modulation by BH3120[3]
(A) Scheme of mouse model used. (B) Tumor volume were measured. Samples were collected 24 hours post 3rd treatment and analyzed for (C,E) cytokine level and for (D, F) T-cell subsets from (C-D) peripheral blood and (E-F) tumor micro-environment.

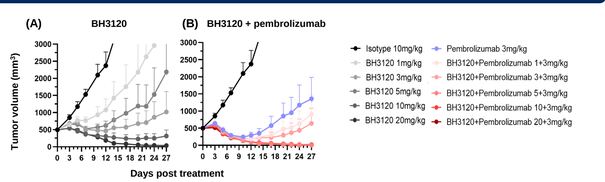


Figure 4. Anti-tumor activity of BH3120 in combination with a PD-1 Inhibitor[4]
Tumor volume from h4-1BB/hPD-1/hPD-1 knock-in mice bearing MC38 hPD-L1 tumor were measured after (A) BH3120 (B) and/or pembrolizumab treatment at indicated time.

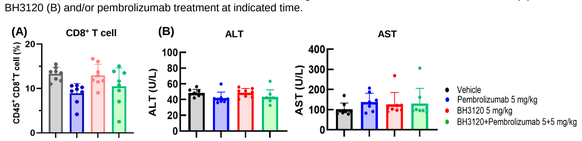


Figure 5. Immune modulation of BH3120 in combination with a PD-1 inhibitor in non-tumor bearing mice[4]
(A) CD8⁺ T cell profile and (B) liver-related enzyme level were measured in non-tumor bearing h4-1BB/hPD-1/hPD-1 knock-in mice after BH3120 and/or pembrolizumab treatment.

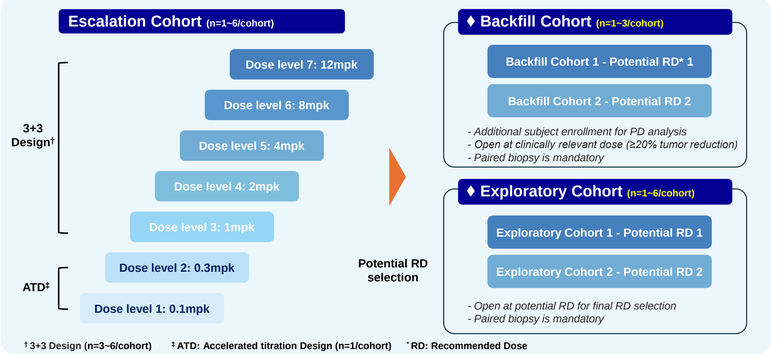
STUDY DESIGN

- This is a Phase I, open-label, multinational, multicenter clinical study enrolling patients with advanced or metastatic solid tumors (NCT06234397).
- BH3120 will be administered via IV infusion at escalating doses on Day 1 of every 3-week cycle (Q3W).
- Backfill Cohorts may be opened for doses at which clinically relevant anti-tumor response is observed.
- Exploratory Cohorts may be opened for potential recommended dose (RD) that is considered for recommended phase 2 dose (RP2D).
- Tumor evaluation will be performed and determined by Investigator using RECIST v1.1 as a primary method.

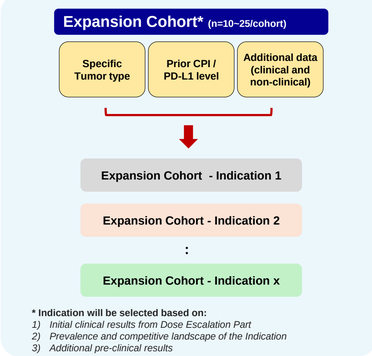
Study Objectives	
Primary	➢ Evaluate safety and tolerability of BH3120
Secondary	➢ Determine Maximum tolerated dose or RP2D of BH3120 ➢ Characterize the pharmacokinetics (PK) of BH3120 ➢ Assess the anti-tumor effects of BH3120
Exploratory	➢ Assess anti-drug antibody response of BH3120 ➢ Assess the pharmacodynamics (PD) response to BH3120 ➢ Explore relation between PK, PD variables, safety and efficacy, if available

Key Eligibility Criteria	
Inclusion	➢ Non-CNS solid tumor that is advanced or unresectable ➢ Failed/are intolerant to standard of care (SOC) ➢ PD-L1 positive expression (TPS≥1% or CPS≥1)
Exclusion	➢ Has received prior anti-4-1BB agents ➢ Immuno-deficient or compromised

► Dose Escalation Part



► Dose Expansion Part



STUDY STATUS

- Phase I study of BH3120 is being conducted in the Republic of Korea (5 sites) and U.S (3 sites).
- First patient was enrolled in February 2024, and the study has enrolled 5 patients to date (September 2024) in Dose Escalation Part.
- BH3120 showed favorable safety profile up to date (September 2024); No Dose-Limiting Toxicities (DLTs) , no treatment-related Serious Adverse Event (SAE), no treatment-related Grade ≥3 Adverse Event (AE) observed.
- Phase I study of BH3120 is currently recruiting subjects in Dose level 4 of the Dose Escalation Part.
- Phase I study of BH3120 will implement additional Arm to assess safety and efficacy of BH3120 in combination with PD-1 inhibitor, pembrolizumab, from 2025. This study is in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA

References

[1] Ochoa. M., et. al. Annals of Oncology (2018) [2] Vinay DS., et. al. BMB Rep (2014) [3] Wang. J., et al. Cancer Res (2023) [4] Wang. J., et al. Cancer Res (2024)

❖ **Hanmi Pharm. Co., Ltd. / kimdw@snu.ac.kr, seongjung.kim@hanmi.co.kr**