A Phase I, Open-Label, Multinational, Multicenter, Dose Escalation and Expansion Study of BH3120, as a Single agent and in Combination with pembrolizumab, in Patients with Advanced or Metastatic Solid Tumor

#325TiP

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BACKGROUND

- 4-1BB (CD137) is a costimulatory receptor that enhances T cell activation and survival, while PD-L1 is an immune checkpoint ligand that suppresses T cell function in the tumor microenvironment[1,2].
- Bispecific targeting of 4-1BB and PD-L1 enables localized T cell co-stimulation while blocking immune suppression, potentially improving anti-tumor efficacy with reduced systemic toxicity.

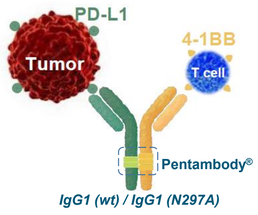


Figure 1. Structure of BH3120

- BH3120 is a bispecific antibody concurrently targeting 4-1BB and PD-L1 to harness this dual mechanism.
- It has been strategically engineered to trigger 4-1BB signal with minimal systemic immune activation, while robustly activating the immune response specifically in the tumor microenvironment[3].
- In preclinical studies, BH3120 monotherapy showed efficient anti-tumor activity with an excellent safety profile, without the risk of cytokine release syndrome or liver-related toxicities[3,4].

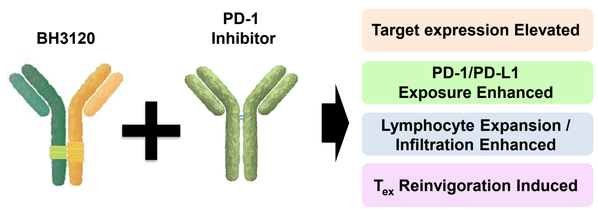


Figure 2. MoA of BH3120 combined with PD-1 inhibitor

- In preclinical studies, BH3120 in combination with pembrolizumab showed similar safety profile and additive anti-tumor efficacy, with the potential to synergize with each other[3-6].
- This is a first-in-human Phase 1 study (NCT06234397) evaluating the safety, tolerability, and preliminary anti-tumor activity of BH3120 as a single agent and in combination with pembrolizumab in patients with advanced or metastatic solid tumors that are PD-L1 positive.
- This study is a multinational, multicenter clinical trial, currently enrolling patients in U.S and Korea

PRECLINICAL HEPATOTOXICITY

Hepatotoxicity is a key safety concern for most of the immunotherapy. Especially, 4-1BB targeting molecules have previously reported severe drug-related hepatotoxicity. Therefore, minimizing the risk of the hepatotoxicity became one of the key factors for designing 4-1BB targeting drugs. BH3120 not only showed favorable liver safety in non-tumor bearing mouse model[4], and tumor bearing mouse models[3], but also in ConA induced hepatitis model which are more prone to liver damage (Figure 3).

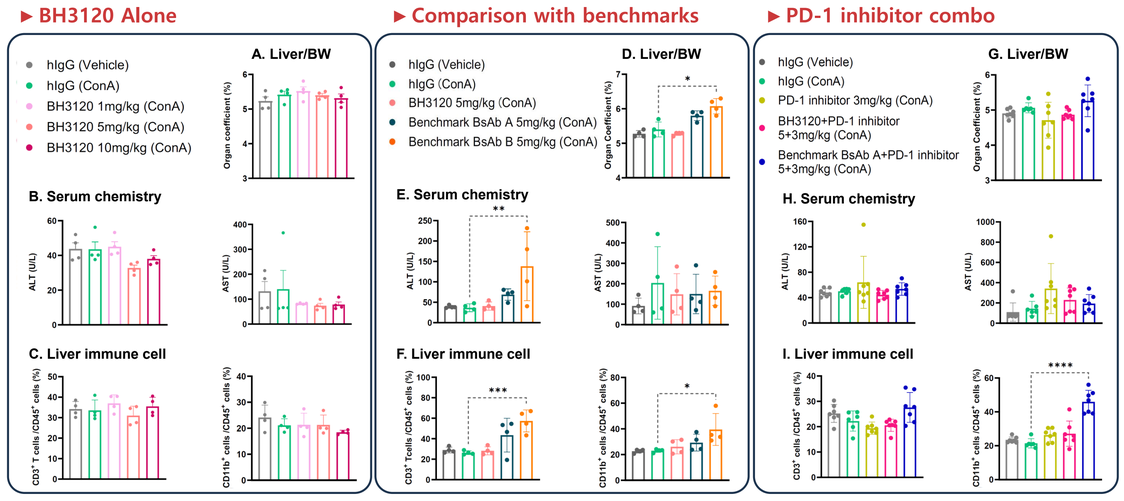


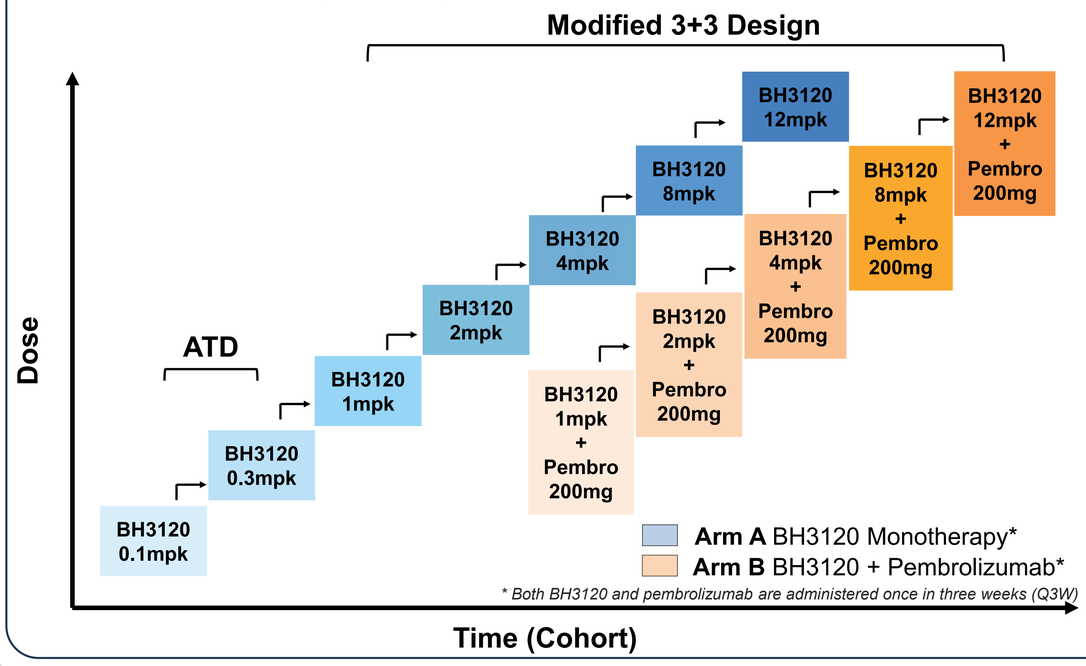
Figure 3. Hepatotoxicity in ConA induced murine hepatitis model[5]

The optimized ConA induced murine hepatitis model was developed and used to evaluate the liver toxicity of BH3120. **(A-I)** Humanized mice (h4-1BB/hPD-1/hPD-L1 knock-in) with optimized ConA conditioning were treated with the indicated antibodies twice a week (BIW, n=3). On day 20, mice were euthanized for collection of liver and blood. The liver-to-body weight ratio (organ coefficient), serum concentrations of ALT and AST, and infiltration of CD3+ T cells and CD11b+ macrophages in the liver were measured. Statistical analysis: **p≤0.01; ***p≤0.001; ****p≤0.0001 vs. ConA model group, one-way ANOVA. PD-1 inhibitor is Pembrolizumab, Benchmark BsAb A and B are biosimilars of GEN1046 and FS222, respectively

STUDY DESIGN

▶ Dose Escalation Part

Escalation Cohort (n=1~6/cohort)



Backfill Cohort (n=1~3/Cohort)

- Backfill Cohort 1 Arm A 4mpk
- Backfill Cohort 2 Arm A 8mpk
- Backfill Cohort 3 Arm A 12mpk (TBD)

- Open at clinically relevant dose (≥20% tumor reduction)
- Paired biopsy is mandatory
- Arm B, Backfill Cohorts can also be opened

Additional clinical data

Exploratory Cohort (n=1~6/Cohort)

- Exploratory Cohort 1 Arm A 4mpk
- Exploratory Cohort 2 Arm A 8mpk
- Exploratory Cohort 3 Arm A 12mpk (TBD)

- Open at potential RD for final RD selection
- Paired biopsy is mandatory
- Arm B, Exploratory Cohorts will also be opened

Potential RD selection

RD Selection

▶ Dose Expansion Part

Expansion Cohort (n=10~25/cohort)

Specific Tumor type | Prior CPI / PD-L1 level | Additional data (clinical and non-clinical)

- Expansion Cohort - Indication 1
- Expansion Cohort - Indication 2
- ▪ ▪
- Expansion Cohort - Indication x

*** Indication will be selected based on:**
1) Initial clinical results from Dose Escalation Part
2) Prevalence and competitive landscape of the Indication
3) Additional pre-clinical results

STUDY OBJECTIVES

Primary Objective

- Evaluate the safety and tolerability of study drugs

Secondary Objectives

- Determine the maximum tolerated dose (MTD) or recommended Phase II dose (RP2D) of BH3120 as a mono- or combination therapy
- Characterize the pharmacokinetics (PK) of BH3120
- Assess the anti-tumor effect of study drugs

Exploratory Objectives

- Assess anti-drug antibody response to study drugs
- Assess the pharmacodynamic (PD) response to study drugs
- Assess the PD-L1 receptor occupancy (RO) of BH3120
- Explore relationships between PK, PD variables, safety, and efficacy, if available

STUDY STATUS

As of 18Sep2025

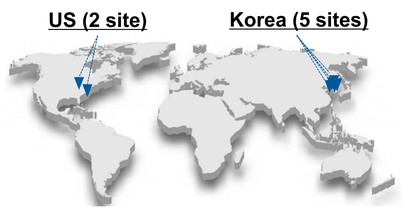


Figure 4. Ongoing study sites

- This is a first-in human, Phase I study of BH3120 as a single agent and in combination with pembrolizumab that is conducted in the Republic of Korea (5 sites) and U.S (3 sites).
- This study is composed of two Parts (Dose-Escalation Part and Dose-Expansion part), and two Arms (Arm A, BH3120 monotherapy and Arm B, BH3120 in combination with pembrolizumab).

Arm A (BH3120 monotherapy)

- First patient was enrolled in February 2024, and total of 23 patients have enrolled in Arm A to date.
- Currently recruiting patients in 12mpk dose Escalation Cohort, and 8mpk dose Backfill Cohort.

Arm B (BH3120 in combination with pembrolizumab)

- First patient was enrolled in March 2025, and total of 8 patients have enrolled in Arm B to date.
- Currently recruiting patients in 4mpk BH3120 in combination with 200mg pembrolizumab dose Escalation Cohort.

Up to date, this study showed favorable safety profile without Dose-Limiting Toxicity (DLT) in both BH3120 monotherapy and pembrolizumab combination therapy. Also, potential anti-tumor effect has been observed with clinically significant tumor response.

In 2026, optimal dose finding for both BH3120 monotherapy and pembrolizumab combination therapy are expected to finish, while Dose-Expansion Part is planned to initiate accordingly.

KEY ELIGIBILITY CRITERIA

Inclusion

- Non-CNS solid tumor that is metastatic or unresectable
- Failed/are intolerant to standard of care
- PD-L1 positive expression (TPS ≥1% or CPS ≥1)
- Adequate hematologic, renal, liver, and anticoagulant function

Exclusion

- Has received prior anti-4-1BB agents
- Known active CNS metastases, that are not stable
- Immuno-deficient or compromised
- Has experienced severe hypersensitivity to any component of the study drugs

ACKNOWLEDGEMENT

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REFERENCES

[1] Ochoa. M., et. al. Annals of Oncology (2018), [2] Vinay DS., et. al. BMB Rep (2014), [3] Wang. Jing., et al. Cancer Res (2023), [4] Wang. Jun., et al. Cancer Res (2024), [5] Wang. Jing., et al. Cancer Res (2025), [6] Wang. Jun., et al. Cancer Res (2025)

FURTHER INFORMATION

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