BH3120 is a bispecific antibody targeting 4-1BB and PD-L1 simultaneously, stimulates T cells in tumor tissue preferred manner

**ABSTRACT**

BH3120 is an IgG1-like bispecific antibody based on Pentamab® platform with biased binding affinities against PD-L1 and 4-1BB. Monovalent anti-4-1BB arm (moderate affinity) and anti-PD-L1 arm (high affinity) together elicited strong antitumor activities in tumor microenvironment (TME), while no significant immune activation was observed in peripheral normal tissues. Antitumor efficacy of BH3120 was in PD-L1 binding and dose-dependent manner without clear hook effect in various models.

Biased binding against each target results in tumor focused distribution of BH3120, and makes TME an ideal environment (PD-L1 high and BH3120 high) for conditionally activation of 4-1BB, while immune poisoning is not observed with immune cells in circulation and liver (PD-L1 low and BH3120 low) of different animal models. The no observed adverse effect level (NOAEL) was determined to be 20 mg/kg without significant systemic immune modulation.

Antitumor activity of BH3120 is further enhanced by synergism with a PD-1 antagonist without additional risk of systemic toxicities indicating clear decoupling of T cell activation between TME and non-tumor tissues, and rapid neutralization of tumor tissue de-rires tumor burden derived inflammation. All these evidences verify the hypothesis that BH3120 stimulates T cells in tumor tissue preferred manner and reduces the risk of systemic immune related adverse events (sAEs).

**Decoupling Tumor and Normal Tissue Study**

- BH3120 with biased binding affinities against PD-L1 and 4-1BB shows preferred distribution in PD-L1 positive tumor tissue (data not shown).
- BH3120 with monovalent anti-4-1BB arm with moderate affinity efficiently co-stimulates tumor cells when PD-L1 expressing tumor.
- In normal tissues, BH3120 does not induce sufficient 4-1BB clustering (hyper-clustering), consequently does not induce functional co-stimulation signatures.

- In PD-L1 low expressing normal tissues (e.g. liver), the PD-L1-IgH-BAAb with high affinity against 4-1BB may result in certain levels of unwanted 4-1BB clustering and subsequent toxicities.
- In low PD-L1 conditions, BH3120 with moderate 4-1BB affinity and biased distribution may avoid excessive 4-1BB agonist and subsequent systemic toxicities.

**Favorable Safety in NHP Toxicity Study**

BH3120 was weekly administered at 36, 100 and 200 mg/kg (D1+W2) in cynomolgus monkey study. No BH3120 related adverse events were found in all treated animals. The NOAEL was determined to be 200 mg/kg without significant systemic immune modulation.

**Conclusion**

In various models studied so far, BH3120 stimulates T cells in tumor tissue preferred manner by biased binding affinities against PD-L1 and 4-1BB.

BH3120 decouples immune modulation in TME from that in normal tissues, consequently decoupling antitumor efficacy from systemic safety issues.

BH3120 in combination with PD-1 antagonist without systemic toxicities.

Clinical evaluation of BH3120 to test the safety and efficacy are planned to be initiated in 2023.