**ABSTRACT**

BH3120 is an IgG1-like bispecific antibody based on Pentamabody® platform with bispecific binding affinities against PD-L1 and 4-1BB. Monoclonal 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.

**Decoupling Tumor and Normal Tissue**

- BH3120 with bispecific binding affinities against PD-L1 and 4-1BB showed preferential distribution in PD-L1-positive tumor tissue (data not shown).
- BH3120 with monospecific anti-4-1BB arm with moderate affinity efficiently co-stimulates lymphocytes in TME.

In normal tissues, BH3120 does not induce sufficient 4-1BB clustering (hyper-clustering), consequently does not induce functional co-stimulation signatures.

**Favorable Safety in NHP Toxicity Study**

BH3120 was weekly administrated at 36, 100, and 200 mg/kg (QW X 5 for non-human primate 4-1BB knockdown monkeys). No unexpected adverse effects were found in all treatments. The NOEL was determined to be 200 mg/kg without significant systemic immune modulation.

**Different Immune Modulation: TME vs. Blood**

<table>
<thead>
<tr>
<th>Immune Activation Stage</th>
<th>TME</th>
<th>Peripheral Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Th cell (CD4⁺) response</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Tc cell (CD8⁺) response</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Decoupling of Efficacy and Hepatotoxicity**

BH3120 shows: (A) Equivalent antitumor efficacy of bispecific antibody with high affinity against PD-L1 without systemic immune related adverse events. (B) No immune modulation by BH3120 in combination with an ICI in non-tumor bearing triple Ki mice. 

**Synergism with an ICI in a Hot Tumor Model**

<table>
<thead>
<tr>
<th>Vehicle</th>
<th>Low CDI</th>
<th>F4/80</th>
<th>BH3120 Combo</th>
<th>GEN1046 Biosimilar Combo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor volume (mm³)</td>
<td>3000</td>
<td>2000</td>
<td>1000</td>
<td>0</td>
</tr>
</tbody>
</table>

**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.