A novel B7-H6/CD3 bispecific IgG-like T cell engaging antibody for the treatment of colorectal cancer

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I have the following financial relationships to disclose:
Employee of Boehringer Ingelheim
Metastatic Colorectal Cancer (mCRC)

- mCRC is the third most common cancer in women and men with 170,000 new cases and 52,980 deaths per year in the United States¹

- Immune therapies have shown limited benefit in mCRC patients²
  - Immune checkpoint therapy is limited to MSI-H CRC patients (~5%)
  - Recent T cell engaging therapies showed adverse events related to normal tissue expression

➢ High medical need to develop novel immunotherapies with high tumor selectivity for the treatment of mCRC

B7-H6 is a Novel Tumor-selective Antigen Expressed in mCRC but not Normal Tissues

B7-H6 mRNA expression in mCRC but not normal colon tissue

Malignant Cancer Gland

Normal Colonic Gland
B7-H6 is a Novel Tumor-selective Antigen Expressed in mCRC but not Normal Tissues

B7-H6 mRNA expression in mCRC but not normal colon tissue

B7-H6 protein expression in mCRC

Normal Colonic Gland

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B7-H6 protein expression in mCRC

Cell surface B7-H6 expression on CRC cell lines
B7-Homolog 6 (B7-H6)

- Single-pass type I membrane protein
- B7 family member
- Low sequence homology (< 20%) to other B7-family members
- Interaction of B7-H6 with NKp30 leads to NK cell activation and cytotoxicity
Molecular Design of B7-H6/CD3 ITE

CD3

Linkers

Engineered Fc

B7-H6

B7-H6/CD3ITE

T cell

Cancer cell

B7-H6
B7-H6/CD3 ITE is a Novel T cell Redirecting Agent

Non-inflamed (‘Cold’) tumor
B7-H6/CD3 ITE is a Novel T cell Redirecting Agent

Proliferating T cells

Activated T cells
Secretion of cytokines

Non-inflamed (‘Cold’) tumor
B7-H6/CD3 ITE is a Novel T cell Redirecting Agent

- Proliferating T cells
- Activation
- Activated T cells
- Secretion of cytokines
- Serial lysis
- Apoptotic cancer cells
- Infiltrating T cells

Non-inflamed (‘Cold’) tumor

Inflamed (‘Hot’) tumor
Selective lysis of B7-H6-positive CRC cell lines

![Graph showing lysis of CRC cell lines in response to B7-H6/CD3 ITE](image-url)
B7-H6/CD3 ITE Induces Potent and Selective T cell Redirected Lysis of B7-H6-expressing CRC Cells *in vitro*

**Selective lysis of B7-H6-positive CRC cell lines**

**High Potency of B7-H6/CD3 at low E:T ratios *in vitro***
B7-H6/CD3 ITE Induces Potent and Selective T cell Redirected Lysis of B7-H6-expressing CRC Cells \textit{in vitro}

Selective lysis of B7-H6-positive CRC cell lines

High Potency of B7-H6/CD3 at low E:T ratios \textit{in vitro}

Relationship between B7-H6 Surface Expression and B7-H6/CD3 ITE Potency
B7-H6/CD3 ITE Treatment Induces Tumor Regressions in NCI-H716 CDX model

**Tumor regressions**

<table>
<thead>
<tr>
<th></th>
<th>q7d</th>
<th>single dose</th>
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<tr>
<td>Day 19</td>
<td>8/9</td>
<td>6/9</td>
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<tr>
<td>Day 28</td>
<td>5/9</td>
<td>1/9</td>
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Treatment with B7-H6/CD3 ITE Leads to Infiltration and Activation of TILs in Tumor Tissue
B7-H6/CD3 ITE Induced Increase of TILs is Associated with Tumor Cell Apoptosis
Summary

- B7-H6 is a novel tumor cell selective antigen expressed with high prevalence in mCRC
- B7-H6/CD3 ITE is a novel IgG-like T cell engager for the treatment of mCRC
- B7-H6/CD3 ITE induces potent and selective T cell redirected lysis of B7-H6-expressing CRC cells but not B7-H6-negative cell *in vitro*
- Treatment with B7-H6/CD3 ITE *in vivo* leads to infiltration and activation of T cells in the tumor tissue resulting in tumor cell death and conversion of a non-inflamed (‘cold’) tumor into an inflamed (‘hot’) tumor
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