Human epidermal growth factor receptor 2 (HER2) is overexpressed in multiple cancers and is associated with poor prognosis. Despite the outstanding improvement in survival with the introduction of anti-HER2 therapies, therapeutic benefit is limited by many resistance mechanisms and toxicities. Monoclonal antibodies targeting HER2 are ineffective in HER2-low cancers, and even though promising results have been obtained using antibody drug conjugates, the impact on survival endpoints has not been established. In addition, clinical trials of therapeutic antibodies targeting HER2 that are safe, promote killing of cancers that are refractory to current therapies and are effective against HER2-low expressing cancers is an unmet medical need.

Using BioAtla’s Conditionally Active Bioactive (CAB) technology1 we developed a Mono-CAB HER2(CD3) (WT-HER2 x CAB-CD3) bispecific antibody that binds with high affinity to recombinant CD3 and induces T cell activation under conditions that mimic the tumor microenvironment (acidic conditions), but with lower affinity in physiological conditions (normal alkaline microenvironment).

The WT-HER2 x CAB-CD3 bispecific antibody is more potent at inducing cytokotoxicity of HER2+ cancer cells in vitro under acidic conditions, and less potent under physiological conditions. Humanized xenograft mouse models of human breast and colorectal cancers treated with WT-HER2 x CAB-CD3 bispecific antibody exhibited complete tumor regression in vivo. Additionally, the anti-tumor activity of WT-HER2 x CAB-CD3 bispecific antibody was observed in both HER2-high expressing BT474 human breast cancer and HER2-low expressing HCT116 human colorectal cancer. A single intravenous bolus administration of WT-HER2 x CAB-CD3 bispecific antibody was well tolerated and overall safe at 0.1 mg/kg in Non-Human Primate (NHP) toxicity studies, with mild clinical pathology changes and cytokine release in contrast to a non-CAB Benchmark HER2/CD3 bispecific antibody.


**INTRODUCTION**

**RATIONALE**

The WT-HER2 x CAB-CD3 bispecific antibody is more potent at inducing cytokotoxicity of HER2+ cancer cells in vitro under acidic conditions, and less potent under physiological conditions. Humanized xenograft mouse models of human breast and colorectal cancers treated with WT-HER2 x CAB-CD3 bispecific antibody exhibited complete tumor regression in vivo. Additionally, the anti-tumor activity of WT-HER2 x CAB-CD3 bispecific antibody was observed in both HER2-high expressing BT474 human breast cancer and HER2-low expressing HCT116 human colorectal cancer. A single intravenous bolus administration of WT-HER2 x CAB-CD3 bispecific antibody was well tolerated and overall safe at 0.1 mg/kg in Non-Human Primate (NHP) toxicity studies, with mild clinical pathology changes and cytokine release in contrast to a non-CAB Benchmark HER2/CD3 bispecific antibody.


**RESULTS**

**CONCLUSIONS**

**DO NOT POST**