A Novel Dual-CAB Nectin-4 x CD3 Bispecific Antibody Targeting Solid Tumors
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INTRODUCTION

Nectin-4 is a predictive marker for cancer diagnosis and a validated therapeutic target. It is believed to play a mechanistic role in cancer metastasis and angiogenesis of several types of primary tumors. Nectin-4 expression has a significant correlation with tumor grade and stages associated to tumor progression. The next generation of anti-cancer therapies targeting Nectin-4 offer the potential to improve patient survival, while reducing harmful side effects.

METHODS

Many therapies targeting Nectin-4 are being developed due to its ubiquitous expression in several types of cancers. These therapies, however, display a high rate of drug related toxicities (due to binding in healthy tissue) accentuating the need for alternative approaches of anti-cancer therapeutics targeting Nectin-4.

Conditionally Active Biologic (CAB) technology is a proprietary platform that allows the generation of bispecific antibodies which have little to no binding to CD3 or the target antigen in healthy tissue (normal alcaline microenvironment). However, in acid conditions that mirror the tumor microenvironment (high glycolysis), the binding of the antibodies to their target molecules is strong. By utilizing BioAtla's CAB platform, we developed a CAB-Nectin-4 x CAB-CD3 bispecific antibody to redirect T-cell activity to the tumor microenvironment.

The CAB-Nectin-4 x CAB-CD3 bispecific antibody was active against Nectin-4 positive human tumor xenografts. Importantly, complete tumor regression was observed upon treatment with CAB-Nectin-4 x CAB-CD3 bispecific antibody. A single intravenous bolus administration of CAB-Nectin-4 x CAB-CD3 was well tolerated and overall safe in non-human primate toxicity studies, with no clinical signs of toxicity.

Reversible CAB bispecific antibodies yield a superior therapeutic index relative to other formats, including produgs.

CONCLUSIONS

• CAB-Nectin-4 x CAB-CD3 bispecific antibodies have increased binding under tumor conditions compared to normal conditions. The pH profile ELISA confirmed the differential affinity with pH ranges from 6.0 to 7.4.

RESULTS

Figure 1. Nectin-4 in the tumor tissues and downstream pathways.

Figure 2. Differential binding profile of non-CAB and dual-CAB Nectin-4 x CAB CD3 by affinity and pH range ELISA.

Table 1. Nectin-4 x CD3 bispecific antibodies induce T cell activation in vitro.

Figure 3. Dose-range efficacy study of the Nectin-4 x CD3 bispecific antibodies using the BT474 MXeno model of human breast cancer.

Table 1. Nectin-4 expressing cells were cocultured with TCR/CD3 expressing cells to express a luciferase reporter driven by NFAT-response element (Promega T Cell Activation Assay). Coecultures were incubated in the presence of Nectin-4 x CD3 bispecific antibodies at pH 6.0 and pH 7.4.

Figure 4. Cynomolgus monkeys received a single intravenous administration of (A) WT-Nectin-4 x WT-CD3 or (B) CAB-Nectin-4 x CAB-CD3 bispecific antibodies. Serum was collected at different time points for cytokine analysis.

Figure 4. IL-6 cytokine levels in the serum of NHP treated with the Nectin-4 x CD3 bispecific antibodies. In non-human primates (NHP), WT-Nectin-4 x WT-CD3 and CAB-Nectin-4 x CAB-CD3 were well tolerated at a dose of 5 mg/kg. WT-Nectin-4 x WT-CD3 bispecific antibody induced high levels of IL-6, while the CAB-Nectin-4 x CAB-CD3 bispecific antibody induced only a mild IL-6 cytokine response at the highest dose level.

• CAB-Nectin-4 x CAB-CD3 bispecific antibodies have similar efficacy in cancer cell line derived MXeno models in vivo compared to the non-CAB benchmark antibodies.

• BioAtla's CAB platform offers the potential to transform bispecific solid tumor therapies through the widening of the therapeutic index.

REFERENCES


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