1343 NOVEL CONDITIONALLY ACTIVE BISPECIFIC HER2 X CD3 T CELL ENGAGER TARGETING SOLID TUMORS

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Background 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. Clinical trials of therapeutics redirecting T cell activity to HER2+ tumors have highlighted the apparent risk of on-target, off-tumor adverse effects for this target, as HER2 is also expressed in normal epithelia.

Methods Using BioAtla's Conditionally Active Biologic (CAB) platform, we have developed a HER2 x CAB-CD3 bispecific antibody that was engineered to bind with high affinity to the CD3 receptor and induce T cell activation under conditions that mimic the tumor microenvironment, but with reduced binding in physiological conditions. Both *in vitro* and *in vivo* efficacy data for a CAB T cell engager (TCE) targeting HER2 will be presented.

Results Our data demonstrate that HER2 x CAB-CD3 bispecific antibody promotes cytotoxicity of HER2+ cancer cells *in vitro* and induces complete regression of tumor growth *in vivo*. The HER2 x CAB-CD3 bispecific antibody has higher potency in inducing primary T cell activation measured by means of cytokine release and cancer cell cytotoxicity under acidic conditions compared to the non-CAB benchmark bispecific antibody. In Non-human primates, the HER2 x CAB-CD3 and a non-CAB HER2 x CD3 were well-tolerated at a dose of 0.1 mg/kg. The non-CAB HER2 x CD3 bispecific antibody induced high levels of cytokines, whereas the HER2 x CAB-CD3 bispecific antibody induced only mild cytokine response.

Conclusions The generation of CAB bispecific antibodies with activity in the disease microenvironment minimizes on-target, off-tumor toxicities, thereby enabling higher potency-TCEs for targeting drug resistant, low expressing-HER2+ tumors. In summary, the use of CAB technology expands the universe of targets for drug development by generating a new class of potent CAB T-cell engagers with increased tolerability for potentially enhanced therapeutic index in the clinic.

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