1005 BIXAB® MAIT ENGAGERS: SOLVING THE PROBLEMS OF CLASSICAL T-CELL ENGAGERS IN THE TREATMENT OF SOLID TUMORS

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Background Mucosal-Associated Invariant T cells (MAITs) are an abundant subset of non-conventional T-cells with potent cytotoxic capacity that are resident in many tissues and solid tumors. T-cell redirection is a clinically validated approach in haematological cancers but has limited success in solid tumors. Classical T-cell engagers (TCE) bind the epsilon chain of the TCR leading to activation of all T-cells. MAIT cells utilize a semi-invariant TCR and Biomunex has generated bispecific antibodies that bind this MAIT semi-invariant TCR (iTCR) and a tumor associated antigen (HER2) to generate BiXAb® MAIT engagers.

Methods Using the Biomunex proprietary BiXAb® platform, bispecific, tetravalent antibodies were generated that target the MAIT iTCR and the HER2 receptor. Binding to proteins and cellular targets was demonstrated by ELISA, DUAL ELISA and FACS. MAIT-cell activation, proliferation and degranulation was followed by gating on MAIT cells within a purified CD8 cell population. Tumor cell lines (varying [HER2]) were co-cultured with MAIT cells and the BiXAb®s in several cytotoxic assays (evaluated by Chromium release). Cytokine release was assessed by Legend Plex assays or ELISA. Cytotoxicity of tumor-resident MAITs was determined from freshly isolated ovarian cancer samples and patient derived 3D organoids were used to assess cytotoxicty and infiltration of peripheral MAITs (The Hub organoids).

Results The BiXAb® MAIT engager efficiently binds both target proteins with similar affinities to the parental Mabs (and binds simultaneously). The MAIT engager binds the MAIT iTCR and can bind cancer cells over a wide range of HER2 expression. BiXAb® engagement of MAIT cells and cancer cells leads to rapid activation, proliferation and degranulation of MAIT cells. At low effector to target ratios (E:T = 2:1), MAIT cells efficiently kill engaged cancer cells (80% cytotoxicity in 18 hrs) with a potency similar to that of a classical TCE (in clinical development). The MAIT engager did not activate the regulatory T cells or other CD4/CD8 subsets. In addition, using PBMCs, total cytokine release was 1000 fold less with the MAIT engager compared to the classical TCE. *Ex vivo* cytotoxicity of tumor-resident MAIT cells using freshly isolated ovarian tumor material and MAIT engager-mediated cytotoxicity of patient derived organoids (Colorectal cancer) will be shown.

Conclusions The tissue/tumor abundance and potent cytotoxic capability of MAIT cells and the specificity of MAIT engagers (no activation of CD4s/Tregs: reduced CRS and immunosuppression) strongly support the contention that MAIT engagers would have a major, durable response in the treatment of solid tumors.

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