

(S189) BTL-101, A FULLY HUMAN TRISPECIFIC BCMA×GPC5D×CD3 T-CELL ENGAGER FOR THE TREATMENT OF MULTIPLE MYELOMA

Topic: 13. Myeloma and other monoclonal gammopathies - Biology & translational research

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Background

Responses to BCMA- or GPRC5D-directed T-cell engagers (TCEs) in relapsed/refractory multiple myeloma (RRMM) can be limited by relapse and antigen escape, supporting dual-antigen targeting while controlling cytokine release to address the unmet medical need for RRMM.

Aims

This study aimed to characterize BTL-101, a fully human trispecific BCMA×GPC5D×CD3 T-cell engager with an affinity-optimized CD3 arm, designed to mitigate relapse and antigen escape in RRMM. Objectives were to define binding to all three targets; evaluate T cell-dependent cytotoxicity across heterogeneous/knockdown antigen expression and under soluble BCMA challenge; assess T-cell activation and cytokine release for a tempered inflammatory profile; and confirm in vivo antitumor activity and tolerability in xenograft and CD3-humanized mouse models.

Methods

BTL-101 is a fully human BCMA×GPC5D×CD3 trispecific antibody with an affinity-optimized CD3 arm. Binding kinetics/affinity were measured by Bio-Layer Interferometry (BLI). T cell-dependent cytotoxicity, activation markers, and cytokines were assessed in Peripheral Blood Mononuclear Cells (PBMC) or whole-blood co-cultures with myeloma cell lines (H929, MM.1S, U266), including soluble BCMA (sBCMA) challenge up to 500 ng/mL. Antitumor activity was evaluated in H929 and MM.1S cell-derived xenografts (CDX); tolerability and cytokines were assessed in CD3-humanized mice.

Results

BTL-101 bound CD3, GPRC5D, and BCMA (KD 40.8, 2.08, and 8.66 nM) and showed faster CD3 on/off kinetics than teclistamab (KD 13.3 nM) and talquetamab (KD 81.4 nM). In myeloma co-cultures (H929, MM.1S, U266), BTL-101 mediated potent killing exceeding talquetamab+teclistamab, depleted dual- and single-antigen-positive cells (including low-to-intermediate BCMA expressers), and retained activity against BCMA- or GPRC5D-knockdown targets, consistent with efficacy under heterogeneous antigen expression. Cytotoxicity remained maximal with soluble BCMA up to 500 ng/mL, whereas teclistamab decreased by ~50%; no binding/cytotoxicity was seen on BCMA/GPRC5D-negative cells. In whole-blood NCI-H929 assays, BTL-101 achieved comparable or superior killing with CD69 activation similar to teclistamab/talquetamab, but generally required higher concentrations to drive deep activation (CD25⁺⁺/CD25⁺⁺CD69⁺⁺) and pro-inflammatory cytokines (eg, IL-6, TNF-α), supporting a tempered cytokine/activation profile. In 48-h PBMC-H929 co-cultures (E:T=5:1), BTL-101 showed higher-potency killing with attenuated cytokines and outperformed JNJ-79635322, SIM0500, and MBS-314. In xenografts, BTL-101 improved dose-dependent tumor control versus vehicle and the talquetamab+teclistamab combination; no observable toxicity and lower cytokines were seen in CD3-humanized mice. A common light chain supports manufacturability (7–8 g/L, >98% purity, stable).

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Summary/Conclusion

BTL-101 demonstrates strong dual-antigen cytotoxicity with an attenuated cytokine profile and resistance to soluble BCMA. A Phase I/II clinical study is currently ongoing to evaluate the safety, tolerability, pharmacokinetics, and preliminary efficacy of BTL-101 in patients with relapsed/refractory multiple myeloma.

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