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Monoclonal Gammopathies & Multiple Myeloma

# UMG1-TRINK15: A FIRST-IN-CLASS TRISPECIFIC NK ENGAGER TARGETING MULTIPLE MYELOMA

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**Background:** Multiple myeloma (MM) is the second most common hematologic malignancy. Despite major advances in immunotherapy, resistance mechanisms such as antigen downregulation continue to limit efficacy, underscoring the need for novel targets. CD43 has emerged as an adverse prognostic marker in MM but is unsuitable for immunotherapy due to its broad expression in normal hematopoietic cells. Conversely, UMG1, a unique CD43 epitope, is selectively expressed on cortical thymocytes and a small subset of peripheral T cells, and absent in other normal tissues, supporting its potential as a safe and specific target. Building on our previous work in T-ALL and DLBCL using UMG1-directed bispecific T-cell engagers, we developed a novel trispecific NK cell engager (TriKE) to exploit NK-mediated cytotoxicity in MM.

**Methods:** We engineered the UMG1-TriNK15 construct comprising one arm targeting CD16 on NK cells, two arms recognizing UMG1 on tumor cells, and an IL-15 linker to promote NK survival and activation. UMG1 expression was evaluated by immunohistochemistry (IHC) on tissue microarrays (TMAs) and by flow cytometry (FC) on bone marrow aspirates from MM patients and established MM cell lines. Cytotoxicity and NK activation were assessed in co-cultures of MM cells with healthy donor PBMCs, exposed to increasing concentrations of UMG1-TriNK15, CD16-IL15 engager, or vehicle. Target cell death was quantified by 7-AAD staining, while NK activation was measured through CD107a degranulation and intracellular IFN-γ expression.

**Results:** IHC analysis revealed UMG1 expression in 51% of MM samples, whereas FC identified expression on 33% of primary CD138$^+$ cells from bone marrow aspirates (3/10 cases). Among MM cell lines, KMS-26 and NCI-H929 displayed detectable UMG1 expression, with KMS-26 showing high surface density. UMG1-TriNK15 treatment induced a strong, dose-dependent NK-mediated cytotoxicity, achieving up to 90% target cell lysis in UMG1$^+$ MM cells at optimal effector-to-target ratios. No cytotoxic effect was observed in UMG1$^-$ cells or with control engagers, confirming the specificity of the response. In parallel, NK activation markers significantly increased, with a 4.5-fold rise in CD107a$^+$ cells and a 3-fold increase in IFN-γ$^+$ NK cells compared to vehicle controls ($p<0.01$). Importantly, UMG1-TriNK15 retained its efficacy using PBMCs from both healthy donors and MM patients, both as single agent or in combination with Lenalidomide, thus supporting potential integration into current therapeutic regimens.

**Conclusions:** Our results demonstrate that UMG1 is expressed in a clinically relevant subset of MM patients and that UMG1-TriNK15 effectively induces potent and selective NK-mediated cytotoxicity and activation. These findings position UMG1-TriNK15 as a first-in-class, off-the-shelf immunotherapeutic agent, paving the way for a biomarker-driven, personalized strategy in the evolving treatment landscape of multiple myeloma.