1379 ENGINEERED TOXIN BODY TARGETING TIGIT DEPLETES TREGS IN THE TUMOR MICROENVIRONMENT AND REDUCES TUMOR BURDEN IN MICE

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Background TIGIT (T cell immunoreceptor with Ig and ITIM domains) is an immune inhibitory receptor, which is known to be over-expressed on Tregs in the tumor microenvironment (TME) of multiple solid tumors and functions as an immunological checkpoint. TIGIT is often co-expressed with PD-1 on Tregs and CD4+ and CD8+ T cells in the TME.[1-3] Monoclonal antibodies (mAb) blocking TIGIT have shown little efficacy as a monotherapy or in combination with αPD-L1 mAb in clinical studies.[4-5] We have shown previously that TIGIT targeting Engineered Toxin Bodies (ETBs) show cytotoxicity in vitro on TIGIT over-expressing cell lines and TIGIT expressing immune cells, including Tregs.[6] Here, we demonstrate the efficacy and pharmacodynamic (PD) effects of TIGIT ETB in a hTIGIT/PD-1 expressing humanized mouse model. Contrary to mAbs, which function by steric hinderance of the TIGIT-CD155 axis, TIGIT ETBs function by direct cell kill of TIGIT expressing cells and represent a novel approach to targeting TIGIT expressing cells in cancers.

Methods MC38 tumor bearing humanized mice (hTIGIT/PD-1) were treated with TIGIT ETB as a monotherapy and in combination with αPD-1 mAb. The effect of TIGIT ETB was compared with αPD-1 and αTIGIT mAbs used alone or in combination. Tumor volumes were measured during the study and all tumors were harvested at study conclusion on day 18 for evaluation of test article effects on tumor immunophenotype.

Results TIGIT ETB monotherapy resulted in the best overall reduction in tumor burden and was comparable with the αPD-1 mAb group. Strikingly, TIGIT ETB monotherapy worked better than the αTIGIT+ αPD-1 mAb combination. TIGIT ETB+ αPD-1 mAb showed similar effects on tumor growth as the αTIGIT+ αPD-1 mAb combination. These effects on tumor growth coincided with significant reduction in Tregs and increased CD8:CD4 ratio in the TME across all TIGIT ETB treatment groups. This TME Treg depletion was not observed with αTIGIT+αPD-1 mAb combination.

Conclusions These data demonstrate that targeting TIGIT using our Engineered Toxin Body platform promotes tumor regression through elimination of TIGIT/PD-1 co-expressing immune cells within the TME. Our data supports using ETB as a monotherapy to target TIGIT and represents a wholly novel approach for modulating TIGIT within the TME.

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