Background The combination of antibody-drug conjugates (ADCs) and immunotherapeutic agents has gained attention due to impressive activity demonstrated in bladder and triple-negative breast cancer. Trastuzumab deruxtecan (T-DXd) is an ADC composed of an anti-HER2 antibody, a cleavable tetrapeptide-based linker, and a cytotoxic topoisomerase I inhibitor approved for HER2+ metastatic breast and gastric cancer. T-DXd has been shown to induce PD-L1 and MHC-I upregulation and demonstrated activity in combination with immune checkpoint inhibitors.\(^1\)\(^2\) We report the result of mechanistic studies of the immune response profile to T-DXd and immune checkpoint inhibitor combinations, utilizing an MMAE containing ADC as a comparator.

Methods Human PBMCs were treated with DXd, MMAE, T-DXd, and T-MMAE (trastuzumab-vc-MMAE) with and without CD3/CD28, and viability measured. Supernatant for coculture assays was collected from human cancer cell lines treated in vitro with T-DXd or T-MMAE. In vivo, BALB/c mice bearing human HER2 expressing EMT6 tumors were treated with T-DXd or T-MMAE +/- anti-PD-L1 mAb and evaluated for pharmacodynamic changes and efficacy.

Results In vitro, treatment of human PBMCs with free DXd caused anti-proliferative effects (IC\(_{50}\) = 0.06\(\mu\)M); however, conjugation of DXd to trastuzumab (T-DXd IC\(_{50}\) = 60\(\mu\)g/mL) mitigated the anti-proliferative effects and was comparable to T-MMAE (IC\(_{50}\) = 12\(\mu\)g/mL). Incubation of human macrophages with supernatant collected from T-DXd treated, but not T-MMAE treated cancer cells resulted in greater than 1.5-fold increase in HLA-DR and CD86 expression, without notable increases in CD163 expression.

In vivo, both compounds exhibited anti-tumor activity in a human HER2-EMT6 tumor model, with treatment resulting in tumor growth inhibition (TGI) of 25.7% (\(P = 0.001\)) for T-DXd, and 11.6% (\(P = 0.123\)) for T-MMAE. In combination with anti-PD-L1 treatment, T-DXd (TGI = 55.4%, \(P < 0.001\)) but not T-MMAE (TGI = 10.8%, \(P = 0.280\)) significantly delayed tumor growth compared to anti-PD-L1 monotherapy (TGI = 16.5%, \(P = 0.063\)). Flow cytometric analysis of T-DXd-treated tumors revealed a significant increase in total CD45\(^+\) cells (1.9-fold, \(P = 0.028\)) and CD8\(^+\) T cells (2.8-fold, \(P = 0.018\)) that was not observed in T-MMAE-treated tumors. T-DXd treatment also promoted a significant increase in tumoral abundance of macrophages (2.2-fold, \(P = 0.001\)), Th cells (2.2-fold, \(P = 0.028\)) and Tregs (2.6-fold, \(P = 0.018\)).

Conclusions These data demonstrate that T-DXd treatment enhances the immunogenicity of human cancer cell lines, promotes tumoral immune cell infiltration, and can be effectively combined with immune checkpoint blockade to enhance antitumor immune responses.

REFERENCES