Development of MGD007, a gpA33 x CD3 bi-specific DART for T-cell immunotherapy of metastatic colorectal cancer

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**Abstract**

Introduction: Encouraging clinical responses have been observed through various strategies designed to harness T-cells for their anti-tumor properties, including immune checkpoint inhibitors, CAR-T cell therapies, and bispecific antibodies. This study was designed to evaluate MGD007, a dual-affinity T cell-redirecting antibody (DART) that promotes cell death through the TNF-related apoptosis-inducing ligand (TRAIL) death receptor pathway. The data demonstrate that MGD007 is well-tolerated, with a favorable PK profile and tumor cell killing properties in vitro. In vivo, MGD007 induces robust and persistent antitumor activity in a preclinical xenograft model.

**Methods:** MGD007 was stably expressed in CHO cells and purified to homogeneity. In vitro functional studies were performed with a range of colorectal cancer cell lines (ST2948, Colo205, and LS174T) and human or cynomolgus monkey T-cells. MGD007 binds CHO cells expressing human or cynomolgus monkey gpA33, but not to untransfected CHO cells. Binding (by flow cytometry) was observed on all 3 human gpA33+ colon cancer cell lines, but not to the gpA33- JIMT1 cells. MGD007 binding to expressing human or cynomolgus monkey gpA33 is a result of the gpA33 target.

**Results:** Following i.p. administration at 20 µg/kg, MGD007 displays consistent antitumor activity in a preclinical xenograft model. Caliper imaging of NSG mice co-implanted SC with Colo205 luciferase-labeled cells and treated with MGD007 (20 µg/kg) or control DART at 10:1 E:T cell ratio with exogenous MGD007 or control DART. Colo205-luc as target cells (24 h; luciferase read out).

**Conclusions:** MGD007 displays potent activity against colorectal cancer cells consistent with a mechanism of action endowed in its design. The gpA33 target was selected based on its ubiquitous expression in colorectal cancer including reactivity with putative cancer stem cell populations (Li 2013, AACR #3763). To enable the degree and type of T-cell infiltration and prognosis suggesting that T-cell recruitment strategies may be particularly advantageous in this type of cancer. We have developed MGD007 as a Dual-Affinity T cell-redirecting antibody (DART) that promotes cell death through the TNF-related apoptosis-inducing ligand (TRAIL) death receptor pathway. The data demonstrate that MGD007 is well-tolerated, with a favorable PK profile and tumor cell killing properties in vitro. In vivo, MGD007 induces robust and persistent antitumor activity in a preclinical xenograft model.

**Keywords:** MGD007, T-cell redirected antibody, colorectal cancer, xenograft model, antitumor activity, TRAIL, dual-affinity T cell-redirecting antibody (DART), gpA33, gpA33 x CD3 bi-specific DART.