ImmuneTherapy of Colorectal Cancer by the T-cell Targeted DART® Protein MGD007: Cellular Mechanisms of Action


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Introduction: MGD007, a bispecific recombinant immunotoxin comprising an anti-gpA33 antibody fragment fused to CD3-TCRαβ mediated T-cell recruitment and redirected T-cell killing of gpA33+ CRC cells, including complete lysis of CRC stem cell-like models. MGD007 activity in CRC cell cytolysis and preclinical PR in nonhuman primates has previously been reported (Cancer Res 2014;74(19) Suppl. Abstract nr 661T). Here we further characterize MGD007 cellular mechanisms associated with redirected T-cell killing, cytokine responses and modulation with standard of care treatments.

Method: Redirected killing assays were performed using luciferase labeled gpA33+ CRC cells or in CRC3D organoid models (CSC-like stem cell subpopulations). Target cell lysates were harvested and quantitated using a luminescence assay.

Results: MGD007 is equally as potent as MGA012 in killing primary cell lines, CRC3D organoid models (CSC-like stem cell subpopulations) and preclinical xenografts in vivo. MGD007 activity in CRC cell cytolysis and preclinical PR in nonhuman primates has previously been reported (Cancer Res 2014;74(19) Suppl. Abstract nr 661T). Here we further characterize MGD007 cellular mechanisms associated with redirected T-cell killing, cytokine responses and modulation with standard of care treatments.

Discussion: MGD007 supports targeted lysis of CRC, including CSC subpopulations previously shown to be resistant to conventional T-cell killing. Additionally, MGD007 also augments cytokine release levels in CRC patients with anti-gpA33 mAb. These findings have important implications for the development of novel immunotherapies for CRC patients.

Key Study Questions:

- How does MGD007 target lysis of CRC cell line models?
- What are the effects of prolonged MGD007 exposure on CRC cell line models?
- What are the effects of steroids on MGD007-mediated biological activity? Do enhanced PD-1 blockade enhance MGD007-mediated anti-tumor activity?

Conclusions:

- Evaluation of MGD007 redirected T-cell killing activity reveals capability to leverage various T-cell populations in combination with anti-PD-1 mAb.
- Greater potency with CD3 vs CD4 T-cell subsets correlates with granularity/phenotypic levels.
- Engagement of CD8 T cells mediated with T-cell lineage cytokine release.
- MGD007 mediates lysis of CRC derived cancer stem cell model cell lines.
- Early cytokine release in presence of MGD007 and gpA33 target cells in vitro exhibit increased levels of tumor cell killing compared to cytokine release.
- Expanded T cells display increased memory phenotype.
- Potential redirected T-cell killing maintained upon re-exposure to MGD007 in presence of gpA33 target cells with limited IL-1β, IL-12 and TNF-α. The mechanism of action of MGD007 in CRC is complex and likely involves multiple cellular and molecular mechanisms. The potency and efficacy of MGD007 in CRC treatment is likely dependent on the specific combination of T-cell populations and their interactions with CRC target cells.