ACTM-838, a Microbial-based Immunotherapy That Enriches in Solid Tumors After IV Dosing, Reverses the Immunosuppressive TME to Promote Durable Anti-Tumor Immunity, Alone and in Combination with Anti-PD1 in Mice

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Abstract

BACKGROUND: Effective treatment of metastatic cancers requires reversal of the immunosuppressive tumor microenvironment (TME) and priming a bystander response to tumor-specific neoepitopes. ACTM-838 is a novel, precision-genome-edited, STIM-dependent STING-Anti-Tumor Cancer Therapy (STACT) strain carrying a DNA-plasmid that encodes the payload L-15 complex (L-15plex) and engineered, constitutively active STING (eSTING). ACTM-838 is designed to colonize the TME and deliver payloads to phagocytic APCs, inducing a durable anti-tumor immune response, after IV dosing.

METHODS: STACT was developed through genome editing of the parental strain, VNMY000. Single-patient (L-15plex or eSTING) STACT strains and ACTM-838 were backcrossed into cell lines and primary immune cells. Uptake, phagocytic expression, and activity were measured in vitro using ELISA, FACS, and flow cytometry. Cytotoxicity was determined by flow cytometry, CLSM, and confocal microscopy. Tumor efficacy was assessed using a mouse mammary tumor model and an orthotopic breast cancer model.

RESULTS: Expression of eSTING L-15plex and eSTING Payloads led to IL-15 secretion and IFN-γ expression, respectively, in cells and primary body macromolecules. STACT immunostaining and eSTING expression were visualized by optical microscopy, single cell analysis, and confocal microscopy. Tumor efficacy was demonstrated in vitro and in vivo in a mouse mammary tumor model and an orthotopic breast cancer model.

CONCLUSION: ACTM-838 delivers L-15plex + eSTING to phagocytic APCs in the TME after systemic administration, leading to potent immune reprogramming. T-cell activation and recruitment promotes durable anti-tumor efficacy as a monotherapy and in combination with anti-PD1 agent delivery. ACTM-838 possesses a compelling safety profile, and is currently being evaluated in a Phase 1 clinical trial.

Synergistic Activity of ACTM-838 in Combination with Anti-PD1 in Two Independent Synergistic Tumor Models

Summary and Conclusions

- ACTM-838 is a STACT that mediates a potent immune response. L-15plex + eSTING is effective in both immune competent and immunocompromised mice.
- ACTM-838 delivers eSTING payload in STING KO BMDMs and induces Activation to a Dual M1/M2 State
- ACTM-838 induces comprehensive and broad reprogramming of the immunosuppressive TME towards an activated anti-tumor immune profile.