1132 IMPACT OF INTRALESIONAL ONCOLYTIC VIRAL THERAPY TARGETING *IN SITU* ACTIVATION OF CD40 AND TYPE 1 INTERFERON SIGNALING PATHWAYS ON THE TME AND SYSTEMIC T CELL IMMUNITY IN MURINE MODELS AND CANCER PATIENTS

[1]Andreas Saltos*, [1]Hong Zheng, [2]Christy Arrowood, [2]Georgia Beasley, [2]James Ronald, [1]Ghassan El-Haddad, [2]Uzma Khan, [1]Luiziane Guerra-Guevara, [2]Steven Wolf, [2]Lin Gu, [2]Xiaofei Wang, [3]Mark Cantwell, [2]Scott Antonia, [1]Amer Beg, [2]Neal Ready. *[1]Moffitt Cancer Center, Tampa, FL, USA; [2]Duke University, Durham, NC, USA; [3]Memgen, Inc, Meadow Vista, CA, USA*

Background Oncolytic viral therapies are thought to act through both direct killing of tumor cells and activation of conventional dendritic cells (cDCs), resulting in an enhanced T cell response. However, cDC activation has not been optimized with current therapies. MEM-288 is a conditionally-replicative oncolytic adenovirus encoding transgenes for human interferon beta (IFNβ) and a recombinant membrane-stable form of CD40-ligand (MEM40), two potent activators of the immune response and cDCs.

Methods We evaluated intralesional adenoviral delivery of MEM40 and IFNβ to activate cDCs in mouse melanoma and lung tumor models. Flow cytometry and scRNA-seq were used to determine treatment impact on cDCs and T cells. Clinical translational research also investigated the immune response of intralesional administration of MEM-288 in patients with select solid tumors in an ongoing Phase 1 dose-escalation, multi-center, open-label trial (NCT05076760). Patient pre- and on-treatment tumor biopsies and peripheral blood were collected before and after MEM-288 treatment for immunologic evaluation.

Results In preclinical studies, MEM40 and IFNβ in situ co-expression induced higher cDC activation than either molecule alone, in addition to a dramatic increase in lymph node migration, a systemic anti-tumor $CD8^+$ T cell response, and regression of established tumors in a manner dependent upon type 1 cDCs. MEM40 and IFNβ expression enhanced generation of both Granzyme B^+ $CD8^+$ T cell effectors as well as $TCF1^+$ stem-like $CD8^+$ T cells that are known to be strongly associated with response to immune checkpoint inhibitors (ICIs). Intralesional therapy with MEM40 and IFNβ expressing adenovirus synergized with ICIs, leading to effective control of distant tumors and lung metastases. Notably, these preclinical results are translating into the clinical setting. Pre- and on-treatment biopsies from the initial 2 non-small cell lung cancer (NSCLC) patients on study were evaluated for TME impact of MEM-288 treatment. A single intralesional injection of low dose cohort MEM-288 (1e10 viral particles) resulted in shrinkage of the injected tumor (-31 and -53%), concomitant with substantial increases in overall $CD8^+$ T cells and $TCF1^+$ stem-like $CD8^+$ T cells. Studies to determine systemic effects on T cells are ongoing.

Conclusions MEM40 and IFNβ expression induces strong remodeling of the TME in both murine models and solid tumor patients. Preliminary safety, antitumor, and immune response data in the ongoing MEM-288 clinical trial is also encouraging. Following completion of the monotherapy study, an expansion arm is planned where MEM-288 will be combined with anti-PD1 antibody in patients with advanced NSCLC refractory to ICI.

Ethics Approval The studies described received IRB approval (Moffitt: Adverra IRB, # Pro00060205, Duke: DUHS IRB, #Pro00109517) prior to commencement, and in the clinical trial described all participants gave informed consent before taking part.

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