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AVM0703 Mobilization of Endogenous Gamma Delta/Invariant TCR+ Bi-Specific Natural Killer T-like Cells Effective Against Solid Tumors and Blood Cancers

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Background: Glucocorticoids (GC) are a common component of blood cancer regimens, typically at doses 40 mg or lower due to concerns of pancreatitis and hepatotoxicity (1,2) and neuropsychiatric effects. AVM Biotechnology has developed a high concentration, high volume, preservative-free, patent pending formulation of dexamethasone (AVM0703), that allows administration of up to 21 mg/kg (1470 mg for 70 kg) over a one-hour IV infusion. Prophylactic use of circadian physiologic hydrocortisone reduces the risk of GC neuropsychiatric side-effects (3,4). Acute supra-pharmacologic doses (>6 mg/kg) AVM0703 mobilizes endogenous bispecific gamma delta invariant TCR+ bi-specific Natural Killer T-like cells (AVM-NKT) (PCT/US21/19773), via a non-GC receptor, that rapidly home to diseased organs in preclinical models and are directly related to tumor killing, including Non-Hodgkin's Lymphoma, Melanoma, and Multiple Myeloma.

1. Walasik-Szemplińska et al. Thyroid Research (2019) 12:13
2. Ataallah et al. Cureus. 2020 Jul; 12(7)
3. Warris, L. T. et al. J. Clin. Oncol. (2016) 34:2287
4. Meijer & de Kloet Endocrinology (2017) 158:448

Methods: Cancer cell lines and (mouse host) were i) immune-resistant mouse A20 B lymphoma (Balb/c), ii) xenografted human T-ALL CCRF-CEM (NCRnu), iii) mouse B16F10 melanoma (B62DF1), and iv) mouse MOPC315 (Balb/c). Cancer cell lines were inoculated into the flank either as single cell suspensions or encased in Matrigel™. When tumor volume reached between 100-500mm^3 well-established tumors, mice were orally gavaged with a human equivalent dose (HED) of 15-18 mg/kg AVM0703 as monotherapy, or as a preconditioning prior to adoptive cell transfer (ACT), or in combination with chemotherapy. Responses were determined by tumor volume measurements, tumor immunohistochemistry or flow cytometry detection of residual cancer cells.

Result: Immunohistochemistry analysis of tumors from AVM0703 treated mice demonstrated pseudoprogression similar to checkpoint inhibitors: *i.e.* tumors were measurable however in some cases all cancer cells had been eradicated. Therefore, subsequent tumor monitoring at end point was done by flow cytometry to quantify the total number of live cancer cells more accurately than tumor measurements by calipers or immunohistochemistry, due to pseudoprogression and limitations of examining only a few sections from each tumor.

Conclusions: AVM0703 led to: i) complete response (CR) in 27% of immune-resistant mouse A20 tumors as monotherapy and CR in 60% when combined with 2 doses of cyclophosphamide/fludarabine (CyFlu); ii) tumor eradication and long-term memory against xenografted human T-ALL; iii) enhancement of ACT equivalent to CyFlu preconditioning in mouse melanoma; and iv) preliminary 95% CR against mouse multiple myeloma.