OVERCOMING IMMUNOSUPPRESSIVE TUMORS BY STIMULATING THE ADAPTIVE AND INNATE IMMUNE SYSTEMS

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Background IL-2 have been approved by the FDA for treatment of metastatic melanoma and renal carcinoma. However, the potent and effective pharmacological activity of IL-2 is limited by its short half-life in circulation and severe adverse effects associated with high systemic exposure. To overcome toxicities associated with systemic administration, intraperitoneal (IP) administration of cytokines has been studied in multiple cancer types. In one study, IP administration of IL-2 in ovarian cancer (n=24) patients resulted in an ORR of 25% (4 complete, 2 partial responses). However, the use of in-dwelling peritoneal catheter required for administration of IL-2 led to a significant complications. Avenge developed the clinically translatable LOCOcyte™ platform to overcome these limitations.

Methods The LOCOcyte™ platform consists of proprietary engineered allogeneic human cells. The cells are encapsulated in a pro-inflammatory biomaterial that are delivered to the local tumor environment and generate high, sustained concentrations. The therapy initiates a robust local and systemic immune response while avoiding toxicities associated with systemic delivery. A library of over 10 cells lines engineered to express cytokines, either individually or in combination, was administered IP in mice and evaluated for anti-tumor activity and immune responses by single-cell RNAseq.

Results Avenge has evaluated the pharmacokinetics and safety of this platform in the both the IP and pleural cavity of rodents in multiple tumor models. Local concentrations are consistently 100x greater than systemic concentrations, demonstrating the ability of the LOCOcyte™ platform to deliver high, localized immune effector concentrations in vivo with limited peripheral exposure. A single administration of AVB-001, engineered to produce native hIL-2, demonstrated complete responses as a monotherapy and provided sustained eradication of ID8 ovarian cancer, MC38 colon cancer and A51 mesothelioma. AVB-001 was also studied in non-human primates (NHP). Single administration of AVB-001 led to therapeutic levels of IL-2 in the IP cavity in NHP and produced local and systemic T cell biomarker profiles predictive of efficacy. Finally, administration of AVB-001 at various doses in NHP in multiple compartments (IP and pleural cavities) were well tolerated at different doses with no signs of toxicities and with no abnormal clinical observations during the study.

Conclusions Findings demonstrate that the LOCOcyte™ platform is safe and efficacious in multiple preclinical animal models. A Phase 1/2 clinical trial of AVB-001 in metastatic peritoneal cancers is actively enrolling (NCT05538624). Our platform enables itself to deliver a diverse set of immunomodulators alone and in combination which is presently being explored.

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