ALG.APV-527: A 5T4 TUMOR DIRECTED BISPECIFIC APPROACH UTILIZING ADAPTIR™ TECHNOLOGY DESIGNED FOR CONDITIONAL 4-1BB T CELL/NK AGONISM AGAINST SOLID TUMORS

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Background 4-1BB (CD137) is an activation-induced co-stimulatory receptor that regulates immune responses of activated CD8+ T cells and NK cells. Leveraging the therapeutic benefit of 1st generation 4-1BB monospecifics has been challenging due to dose limiting hepatotoxicity. To minimize systemic immune toxicities and enhance activity at the tumor site, we have developed a novel 4-1BB x 5T4 bispecific antibody that stimulates 4-1BB function only when co-engaged with 5T4, a highly selective tumor-associated antigen. The combined pre-clinical dataset presented here provides an overview of the potential indication landscape, mechanism of action and the efficacy and safety profile of ALG.APV-527, supporting its advancement into the clinic.

Methods Genevestigator Software was used to analyze curated transcriptomic data from bulk tumor mRNA-sequencing data libraries and from single cell RNA-seq libraries for the expression profiles of CD8, 4-1BB and 5T4 across selected human solid tumor datasets. ADCC and ADCP reporter bioassays were utilized to assess Fc engagement by ALG.APV-527. For in vitro tumor lysis studies, human T cells were co-cultured with labelled tumor cells and sub-optimally activated with anti-CD3. Cytotoxicity of tumor cells were continually assessed using a Live-Cell Analysis System.

Results Dual expression of CD8 and 5T4 occurred in many tumor types and correlated well with indications that are pursued in the clinical development of ALG.APV-527. 4-1BB expression was observed in tumor-derived lymphoid subpopulations, especially in those with an exhausted phenotype. Since ALG.APV-527 is designed with a non-Fcγ receptor binding Fc, minimal ADCC & ADCP was induced in vitro. Additionally, ALG.APV-527 enhanced primary immune cell-mediated killing of 5T4-expressing tumor cells when compared to anti-CD3 alone, demonstrating the potential benefit of 4-1BB agonism for enhancing cytotoxic anti-tumor responses in the clinic.

Conclusions

ALG. APV-527 is designed to elicit safe and efficacious 4-1BB-mediated antitumor activity in a range of 5T4-expressing tumor indications. Transcriptional profiling of patient tumor samples demonstrates 4-1BB expression in multiple tumor-infiltrating lymphocyte subsets and identifies potential indications with 5T4 expression and CD8+ T cell infiltration. The unique design of the molecule minimizes systemic immune activation and hepatotoxicity, allowing for highly efficacious tumor-specific responses as demonstrated by potent activity in in vitro models. Based on these preclinical data, ALG.APV-527 is a promising anti-cancer therapeutic for the treatment of a variety of 5T4-expressing solid tumors and is progressing towards a phase I clinical trial in 2021.

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