**Introduction**

- **4-1BB (CD137)** is an activation-induced costimulatory immune receptor expressed on tumor-infiltrating T cells and NK cells.
- **Stimulation of 4-1BB leads to enhanced proliferation, increased survival, intensified cytokine production, and enhanced IFN-γ production of T and NK cells.**
- **4-1BB-targeting immunotherapies have shown promising anti-tumor effects clinically however, a monospecific 4-1BB agonist induced dose-limiting hepatic toxicities.**

- **5T4 is a tumor-associated antigen expressed in a variety of malignancies, including NSCLC, head and neck, mesothelioma, renal, pancreas, bladder, breast, colorectal, gastric, ovarian and cervical cancers.**

**About ALG-APV-527**

- **ALG-APV-527 is an ADAPTIR™ bispecific therapeutic containing two sets of scFv binding domains targeting 5T4 and 4-1BB, linked to an effector-null Ig Fc domain.**
- **The scFvs originate from the Alligator Gold® human scFv library (Alligator Bioscience) and have been optimized for use in the bispecific ADAPTIR™ format (Apteva Therapeutics).**
- **ALG-APV-527 features target-driven T cell stimulation, optimized stability, good manufacturable properties with potential for better risk-benefit in humans than other monospecific 4-1BB antibodies.**
- **ALG-APV-527 is cross-reactive to 4-1BB and 5T4 from cynomolgus monkey. It enhances stimulation of CD3-activated human and cynomolgus T cells in vitro.**
- **ALG-APV-527 has an antibody-like in vivo half-life.**

**ALG-APV-527 Mode of Action**

- **ALG-APV-527 directs the stimulation of CD8+ T and NK cells by 5T4+ tumors and is designed to minimize the toxicity observed with other 4-1BB therapeutics.**
- **IL-2 upregulates 4-1BB expression on NK cells.**
- **Titration of ALG-APV-527 in the presence of 5T4-expressing tumors enhances secretion of cytokytic molecules such as IFN-γ and Granzyme B (GzmB) and promotes proliferation.**
- **Stimulation of T cells with anti-CD3 induces the upregulation of 4-1BB. Addition of ALG-APV-527 to 5T4+ tumors augments primary CD8+ T cell proliferation and secretion of IFN-γ.**
- **ALG-APV-527 induces the generation of memory cells.**
  - **(A) Day 0: MB49 cells expressing human ST4 were injected into 4-1BB knock-in mice. Starting on day 5, treatments of ALG-APV-527 were administered IP once weekly until day 28 of mice treatment.**
  - **(B) Surviving mice that had cleared their primary tumor were re-challenged with MB49 tumor cells on day 80.**

**Summary and Conclusions**

- **ALG-APV-527 has a favorable non-clinical safety profile with no indications of systemic activation or liver toxicity in NHP or murine models.**
- **The combination of CD8+ T cells and anti-CD3 scFv molecules, ALG-APV-527, has the potential to be a unique anti-cancer therapeutic agent with an improved safety profile for the treatment of numerous 5T4-expressing solid tumors with unmet medical need.**
- **CTA documents are prepared for filing of a phase 1 clinical trial.**