673: Preliminary results from a phase I dose escalation study of ALG.APV-527, a 5T4 x 4-1BB bispecific antibody, in patients with advanced solid tumors demonstrate favorable safety and biological activity

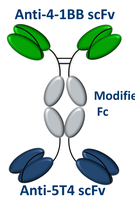
Thomas Marron[1], Seth Rosen[2], Douglas Orr[3], John Powderly II[4], Jennifer Segar[5], Noor Khaskhely[6], Lynn Bonham[6], Michelle Nelson[6], Caroline Taromino[6], Daphne Taylor[6], John Kumer[6], Ashley Milton[7], Peter Ellmark[8,9], Sara Fritzell[8], Sumeet Ambarkhane[8], Dirk Huebner[6], Asrar Alahmadi[10]

1.Tisch Cancer Center, Icahn School of Medicine at Mount Sinai, New York, NY, USA; 2.Hematology Oncology Associates of the Treasure Coast, Port Saint Lucie, FL, USA; 3.Mary Crowley Cancer Research, Dallas, TX, USA; 4.Carolina BioOncology Institute, Huntersville, NC, USA; 5.University of Arizona Comprehensive Cancer Center, Tucson, AZ, USA; 6.Aptevo Therapeutics, Seattle, WA, USA; 7.KHM Pharma Consulting, Massachusetts, USA; 8.Alligator Bioscience AB, Lund, Sweden; 9.Department of Immunotechnology, Lund University, Lund, Sweden; 10.Ohio State University Comprehensive Cancer Center, Columbus, OH, USA

Acknowledgements: We would like to thank Sarah Jones, Likiso Nyambi and Jennifer Price for pharmacology data analysis, Sirona Dx for IMC, Rules Based Medicine s41BB and PPD for PK testing.

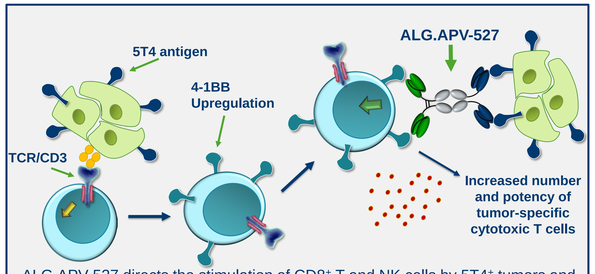
About ALG.APV-527

- ALG.APV-527 is a bispecific therapeutic containing binding domains targeting the co-stimulatory receptor 4-1BB and the oncofetal antigen 5T4, expressed on multiple solid tumor types. These are linked to an effector-null Ig Fc domain, providing an antibody-like *in vivo* half-life
- The scFvs originate from the Alligator Gold® human scFv library (Alligator Bioscience) and optimized for use in the bispecific ADAPTIR™ format (Aptevo Therapeutics)
- ALG.APV-527 features targeted T cell stimulation, optimized stability, good manufacturing properties with potential for better risk-benefit in humans than monospecific 4-1BB antibodies



- Published preclinical studies demonstrate the design and mechanism of action of ALG.APV-527.
  Mol Cancer Ther. 2023 Jan 3;22(1):89-101. doi: 10.1158/1535-7163.

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

Study Design

The Phase I study is a first-in-human, open-label, multicenter trial consisting of up to six cohorts (0.1-15 mg/kg) with a 3+3 dose escalation of ALG.APV-527 monotherapy, administered IV Q2W, in adult patients with advanced solid tumors. Eligibility is limited to patients with tumor types identified as likely to express 5T4 antigen.

Clinical Trials Number: NCT05934539

Key Objectives

- Characterize **safety & tolerability profile** of **ALG.APV-527**
- Identify **MTD** and/or **RP2D**
- Characterize **PK profile** after single and repeated IV administration
- Assess potential **immunogenicity** effects
- Obtain a preliminary assessment of **anti-tumor activity**

Baseline Characteristics

Dose (mg/kg) Total n=18	Median age (range)	Gender (%) F	Gender (%) M	ECOG PS (%) 0	ECOG PS (%) 1
Cohort 1 0.1 (n=4)	75.5 (71-82)	2 (50)	2 (50)	0	4 (100)
Cohort 2 0.5 (n=3)	58.0 (56-74)	1 (33)	2 (67)	0	3 (100)
Cohort 3 2.0 (n=6)	56.5 (39-72)	5 (83)	1 (17)	2 (33)	4 (67)
Cohort 4 6.0 (n=3)	47.0 (44-60)	2 (67)	1 (33)	1 (33)	2 (67)
Cohort 5 12.0 (n=2)	56.0 (51-61)	2 (100)	0	0	2 (100)

Prior Anti-Cancer Therapy	n (%); median (range)
Surgery	8 (44); 1 (1-3)
Radiotherapy	12 (67); 1 (1-3)
Systemic Therapy	18 (100); 6 (2-8)

Prior Systemic Therapy	n (%)
Chemotherapy & other antineoplastic therapies	18 (100)
Immune and antibody therapies*	13 (72)

n= number of patients; *bevacizumab (8), pembrolizumab (3), nivolumab (2), ipilimumab, IL-2, cetuximab, panitumumab, durvalumab, cemiplimab

Treatment-Related AEs

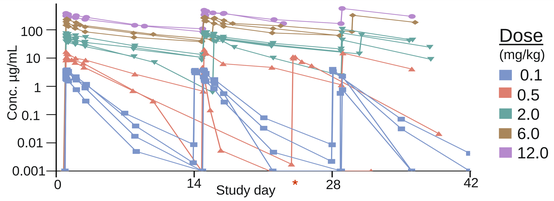
>1 Patient 18 total patients	n (%) E
Any TRAE	16 (89) 92
Fatigue	4 (22) 6
Infusion-related reaction	4 (22) 7
Diarrhea	3 (17) 4
Pruritus	3 (17) 4
Nausea	2 (11) 2
ALT increase	2 (11) 2
Anemia	2 (11) 4
Neutrophil count dec.	2 (11) 2
WBC count decrease	2 (11) 3
Myalgia	2 (11) 2
Dyspnea	2 (11) 3

Serious Treatment-Related AEs	n (%) E
Any Serious TRAE	4 (22) 5
Febrile neutropenia*	1 (6) 1
Ulcerative colitis	1 (6) 1
Hemorrhagic diarrhea	1 (6) 1
GI hemorrhage	1 (6) 1
Nausea	1 (6) 1

Overall, ALG.APV-527 was safe and well tolerated. No severe signs of liver toxicity were seen to date.

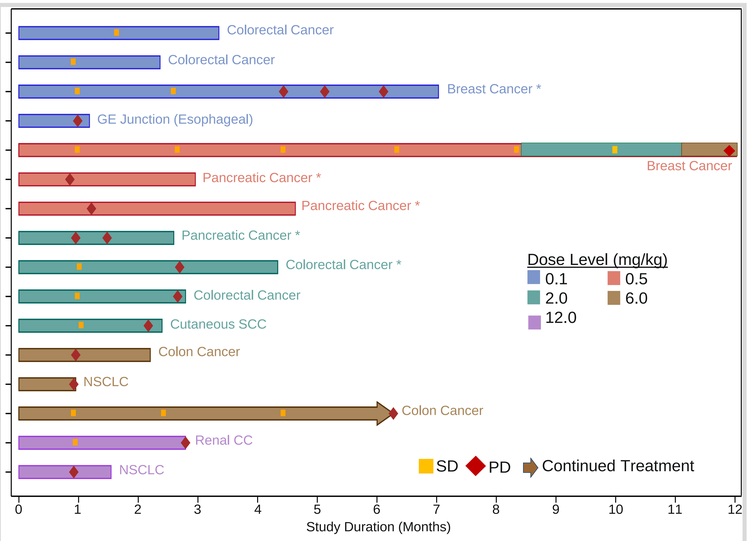
*Case of Gr4 febrile neutropenia, classified as a DLT, and resolved following Filgrastim treatment. n= number of patients, E= number of events

PK is proportional to dose and linear over time



ALG.APV-527 displays a dose-dependent PK, faster clearance following the lower doses, though linearity is evident over time; the drug is detectable in the serum of all tested patients similar to the human PK predicted exposure. Data displayed through cycle 3. *One Cohort 2 patient C2D1 dose delayed 10 days to study day 24

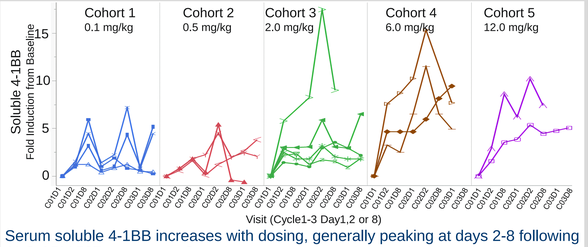
Duration on Study



Sixteen of 18 patients were evaluable at data cutoff (12Sept2024). Based on RECIST and iRECIST, nine patients had a best overall response of SD. The dose administered to the breast cancer patient in cohort 2 was escalated from 0.5 to 2.0, then to 6.0 mg/kg after long-term SD.

SD= stable disease, PD= progressive disease *Patients were allowed to stay on study with PD events if agreed upon with the treating physician

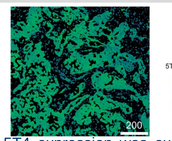
Increased soluble 4-1BB in blood following ALG.APV-527 treatment



Serum soluble 4-1BB increases with dosing, generally peaking at days 2-8 following ALG.APV-527 treatment. Samples were evaluated using Luminex technology and graphically represented as fold change from baseline.

All tumor types from all subjects expressed 5T4

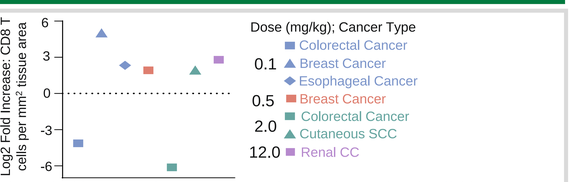
Cancer type	5T4 (intensity*)
Colon Cancer	Positive (144)
Breast Cancer	Positive (109)
Esophageal Cancer	Positive (100)
Breast Cancer	Positive (182)
Pancreatic Cancer	Positive (203)
Pancreatic Cancer	Positive (231)
Colon Cancer	Positive (213)
Colorectal Cancer	Positive (211)
Colon Cancer	Positive (223)
Cutaneous SCC	Positive (266)
Colon Cancer	Positive (137)
NSCLC	Positive (234)
NSCLC	Positive (204)
Renal Cell	Positive (230)



5T4 expression was examined in tumor biopsies by IMC: 5T4 was detected in all evaluable samples and tumor types (table). An example of a breast cancer patients' screening biopsy for 5T4 (image).

*5T4 scoring was conducted utilizing the modified histoscore, providing a semiquantitative assessment of both staining intensity and the percentage of positive cells.

ALG.APV-527 treatment results in an overall increase in number of CD8 T cells in the TME



Eight evaluable pre- and post-treatment* (Cycle 3/Day 1 (+2 days)) biopsies were examined by imaging mass cytometry (IMC) and the number of tumor infiltrating CD8 T cells is displayed.

*One sample had no detectable CD8 T cells post-treatment in the region of interest and is therefore not included in this log-fold change graph.

Summary and Conclusions

ALG.APV-527 demonstrates good tolerability, safety, and evidence of biological activity. The dose escalation is ongoing. An MTD has yet to be determined.

> Serum soluble 4-1BB increased with dosing and tumor infiltrating CD8 T cells increased in most post treatment samples.

> No serious liver toxicity occurred with this conditional 4-1BB bispecific likely due to its TME-specific activating design.

> Serum concentrations of ALG.APV-527 were consistent with the administered dose.

> Nine of 16 evaluable patients (56%) had a best overall response of SD, with the longest SD duration in a breast cancer patient >11 months. One MSS colon cancer patient with sustained SD remains on study.

Presented at the Society of Immunotherapy in Cancer (SITC) Annual Meeting, Houston, TX, 08November2024