APVO603: A dual 4-1BB and OX40 bispecific approach utilizing ADAPTIR™ platform technology designed to deliver a conditional T cell/NK response against solid tumors

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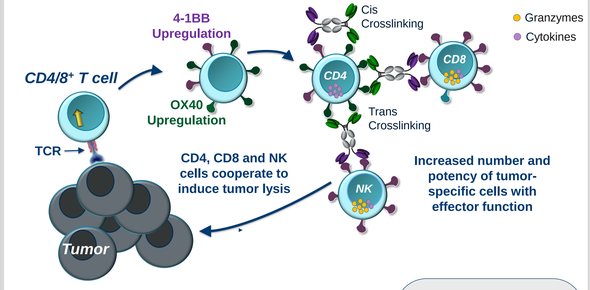
APVO603 (α4-1BB x αOX40), a Dual Costimulatory Molecule Designed to Treat Multiple Solid Tumors

Therapeutic Candidate	• Next generation ADAPTIR for T-cell and NK-cell costimulation • Mutated IgG1 Fc; No ADCC or CDC; retains FcRn binding
Mechanism of Action Benefits	• Activity non-dependent on direct engagement of a tumor antigen • Potential to enhance the tumor microenvironment (TME) responses: Reduction/reversal of suppressive environment; Limitation or reversal of T cell exhaustion • Designed for enhanced effector function and survival of pre-existing TIL and NK cells
Potential Safety Benefits	• Requires engagement of both 4-1BB and OX40 in cis or trans to induce downstream signaling (tumor-dependent response) • 4-1BB and OX40 are expressed on activated lymphocytes and relatively few peripheral lymphocytes. Increased potential to target tumor infiltrating lymphocytes (TIL)
Indications	• Multiple inflamed solid tumor types with resident tumor infiltrating T cells (such as NSCLC, RCC) • Potential to combine with checkpoint inhibitors
Half-life	• 5.5 days in mice; up to 4.8 days in NHP • Fully cross-reactive with cynomolgus macaque
Development Stage	• Preclinical; IND-enabling studies underway • CMC activities in progress to support IND filing in 2022

APVO603 is Designed to Potentiate Memory Generation & Tumor Lysis in Recently Activated TIL



Potential Key Advantages for APVO603

- APVO603 is a novel ADAPTIR bispecific with a unique mechanism of action (MOA) that may boost natural antitumor responses by activating two different costimulatory receptors
- APVO603 enhances effector lymphocyte populations (CD4, CD8 & NK cells) via increased proliferation, amplified cytokine production and cytolytic capacity
- APVO603, was designed as a conditional activator with potential to reduce toxicities observed for competitor 4-1BB mAbs with the potential to reinvigorate immune responses and enhance prolonged tumor rejection in multiple solid tumor indications

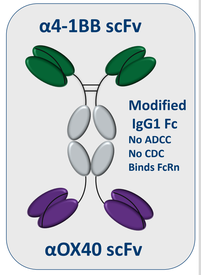


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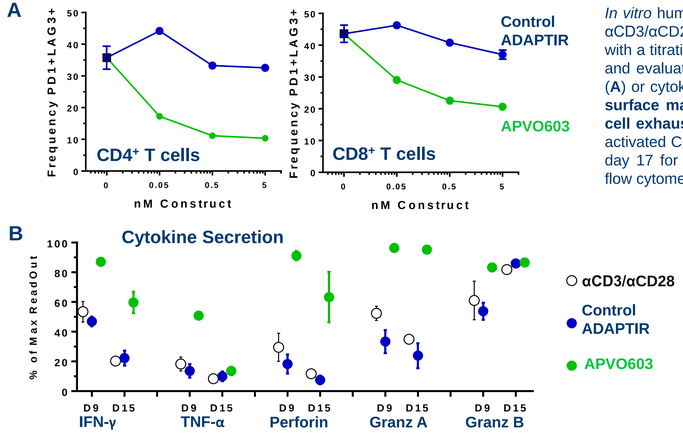
Fig.1 APVO603 Reduces T Cell Exhaustion Markers & Prolongs Cytokine Secretion



In vitro human T cell cultures were activated with αCD3/αCD28 on days 0, 2, 6, 9, 12 and 15 along with a titration of APVO603 or a control ADAPTIR and evaluated for surface markers of exhaustion (**A**) or cytokine secretion (**B**). **APVO603 reduces surface marker expression associated with T cell exhaustion.** For surface marker expression, activated CD4⁺ or CD8⁺ T cells were analyzed on day 17 for co-expression of LAG3 and PD-1 by flow cytometry.

APVO603 costimulation treatment augments cytokine secretion in restimulated cells. Sups from D9 or D15 reactivated cells were analyzed for cytokine secretion via multiplex-based assay (Milliplex). 0.5 nM of control or APVO603 were compared to αCD3/ αCD28 treatment only.

These data suggest that the costimulatory effects of APVO603 may diminish the detrimental & exhaustive effects of repeated stimulation within the TME.

Fig. 2 APVO603 Augments Rejection of Established Tumors & Enhances Survival

APVO603 significantly reduces MB49 tumor burden *in vivo*. Human 4-1BB /Human OX40 knock-in mice were implanted with the human bladder cancer line, MB49, and tumors allowed to establish for 6 days prior to twice-weekly therapeutic treatment. Mean tumor volume for each group is plotted ± SEM. Compared to PBS, APVO603 at 90 & 30 μg was significant. Mean 8 mice/ group.

These data demonstrate that MB49-specific lymphocytes gain cytolytic capacity following APVO603 treatment that leads to reduced tumor burden and prolonged animal survival. These effects were significantly better when compared to the 4-1BB monospecific urelumab analog.

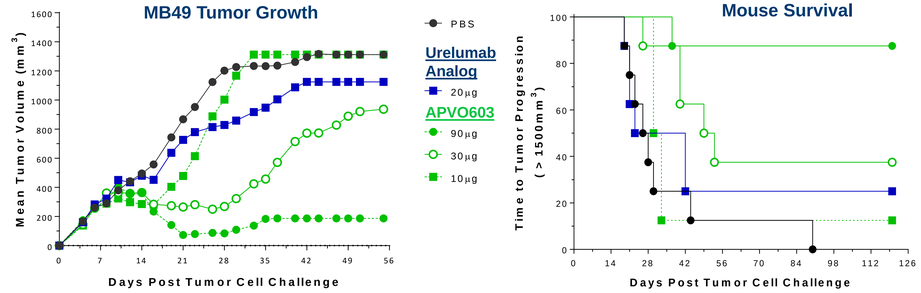
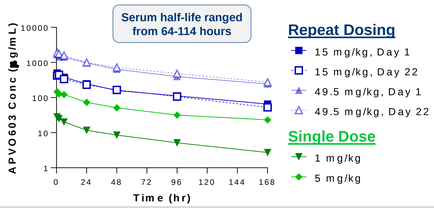


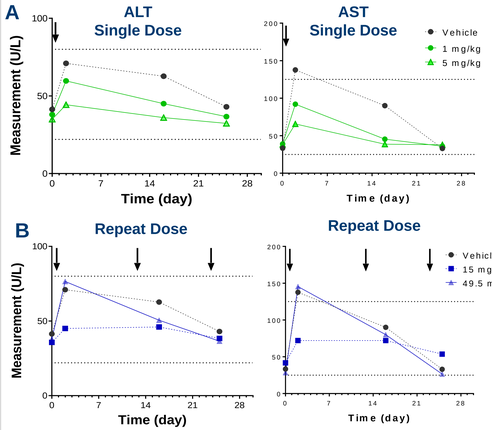
Fig. 3 APVO603 has a Favorable Antibody-Like Half-Life in Non-Human Primates



NHP pharmacokinetic data for APVO603 had dose proportional concentrations. APVO603 serum concentrations were measured in cynomolgus monkeys (n=3 per group) following single or multiple weekly doses. Based on non-compartmental analysis (NCA), the serum half-life of APVO603 was in the range of 64 - 114 hr. Mean systemic exposure increased with dose in a dose-proportional manner, based on Cmax and AUC, and no significant accumulation was observed after repeat dosing (Day 22) compared to a single dose (Day 1). NCA was conducted using data through 168 hr post-dose.

The PK profile of APVO603 in NHP supports clinical dosing.

Fig. 4 APVO603 Has a Favorable Safety Profile in Non-Human Primates



The preliminary safety of APVO603 was evaluated in a non-GLP toxicology study performed in cynomolgus monkeys. Single dose and repeat-dose groups were included in the study. APVO603 was administered by intravenous bolus infusion. Samples were collected throughout the study for clinical pathology, PK, ADA, and immunophenotyping by flow cytometry. Repeat-dose animals were evaluated at necropsy following Day 28 for histopathology with no evidence of liver toxicity.

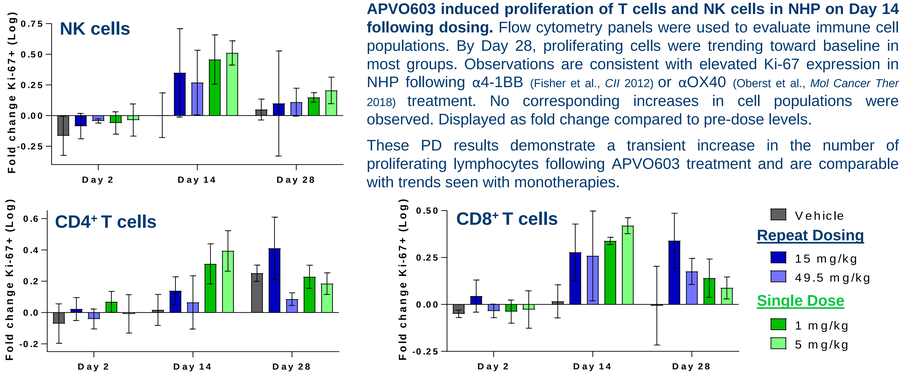
Findings from the non-GLP toxicology study

- APVO603 administration was well tolerated in animals at all dose levels.
- Clinical pathology evaluations included all standard hematology, coagulation and clinical chemistry parameters, with no indication of adverse reactions based on the MOA.
- No cytokines were detected following the first dose for any animal in single or repeated-dose groups.

Liver enzyme levels were not impacted by APVO603. Samples were collected pre and 24 hours post relative to dosing on Day 1 and 15 and then on Day 25. No general elevation in liver enzymes by single dose (**A**) or repeat-dose (**B**) were observed during treatment. The observed changes were not considered dose-dependent for APVO603 and were similar to the vehicle control group. Dotted line is the range for Cambodian Male NHP (Wilcox, et. al., SOT 2015).

These data demonstrate that APVO603 treatment does not induce hepatotoxicity and did not induce adverse reactions in NHP.

Fig. 5 APVO603 Elicits an OX-40/4-1BB Associated PD Response in NHP



APVO603 induced proliferation of T cells and NK cells in NHP on Day 14 following dosing. Flow cytometry panels were used to evaluate immune cell populations. By Day 28, proliferating cells were trending toward baseline in most groups. Observations are consistent with elevated Ki-67 expression in NHP following α4-1BB (Fisher et al., *CII* 2012) or αOX40 (Oberst et al., *Mol Cancer Ther* 2018) treatment. No corresponding increases in cell populations were observed. Displayed as fold change compared to pre-dose levels.

These PD results demonstrate a transient increase in the number of proliferating lymphocytes following APVO603 treatment and are comparable with trends seen with monotherapies.

Summary and Potential Advantages of APVO603

- APVO603 may reduce or reverse negative effects of T-cell exhaustion and suppressive immune responses by augmenting cytokine production and reducing markers of T cell exhaustion following repeat stimulation *in vitro*
- APVO603 therapy induces a dose-dependent *in vivo* antitumor responses and significantly increases the survival in MB49-inoculated mice
- APVO603 was well tolerated in NHP with a favorable safety profile (up to 50 mg/kg) without liver toxicity

	4-1BB mAb	OX40 mAb	APVO603 Bispecific
Safety	Liver toxicity (4-1BB superagonist)	Good safety profile in NHP and Humans	Bispecific targeting requires dual 4-1BB and OX40 expression and limits on target toxicity
Efficacy	Potent agonist, limited by therapeutic index	Lack of clinical response as single agent	Bispecific targeting allows for cis/trans engagement of T cells for enhance potency