KVA12123: an anti-VISTA monoclonal antibody with strong single agent anti-tumor activity and no evidence of cytokine mediated toxicity

#425

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Introduction

- VISTA (V-domain Ig Suppressor of T cell Activation) is a unique CD28/B7 family member with poorly defined receptors. However, PSGL-1, VSIG3, VSIG8, LRIG1 and VISTA itself have been suggested as putative receptors
- VISTA is highly expressed on circulating and intratumoral myeloid cells
- VISTA is a negative regulator that suppresses T cell activation and proliferation
- High VISTA expression correlates with poor survival in cancer patients
- VISTA is a unique immune checkpoint inhibitor for tumor immunotherapy

Background

- 107 fully-human scFv anti-VISTA antibodies were generated and analyzed
- The wild-type (WT) IgG1-Fc of KVA12104 was optimized to obtain our clinical lead, KVA12123
- KVA12123 is highly specific, has extended PK, reduced ADCC and binds to a unique VISTA epitope
- KVA12123 activates monocytes, and this activation is NK dependent
- KVA12123 reverses MDSC suppression of T cells
- KVA12123 binds to human and cynomolgus VISTA with similar affinity

Objectives

- KVA12123 IgG1-Fc region has been optimized (YTE) to improve PK and reduce ADCC, and was compared to published anti-VISTA antibody VSTB174
- KVA12123 anti-tumor response has been evaluated as a single-agent or in combo-therapies (e.g. anti-PD1) in multiple mouse tumor models
- Safety and tolerability of our clinical lead KVA12123 have been evaluated

KVA12123 antibody induces strong anti-tumor response as a single agent or in combo-therapies

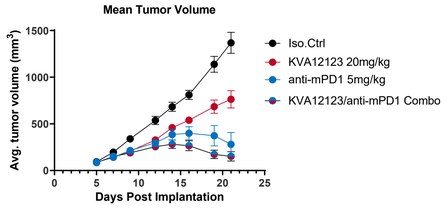


Figure 1. 5e5 MB49 cells were inoculated in the right flank in female hVISTA Knock-in (KI) mice. On Day 5 when tumors reached 70-100 mm3, mice (n=8) were administered 20 mg/kg KVA12123 or isotype control (human IgG1) alone or in combination with anti-mPD-1 (5mg/kg) every 3-4 days for three weeks by IP injection. Tumor volumes were measured at least three times a week. Data shows mean tumor volumes over time. Error bars represent SEM.

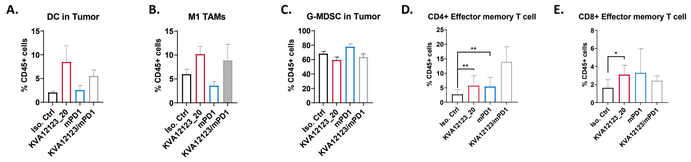
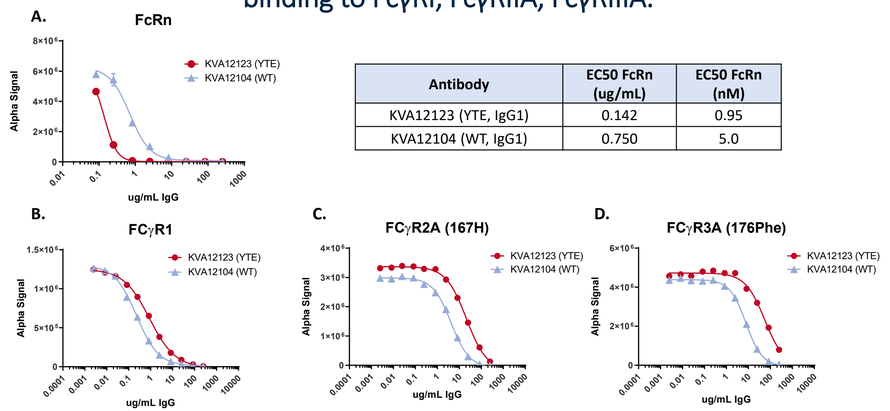


Figure 2. Immunophenotyping of leukocytes infiltrating KVA12123-treated tumors shows a shift from an immunosuppressive to a proinflammatory Tumor Micro-Environment. (A-E) MB49 bladder carcinoma tumor TMEs in hVISTA KI mice were assessed to define infiltrating immune cells by FACS. Data shown are mean values (n= 3-6 mice) for each group. Error bars represent SEM and p value was obtained by unpaired t-test. *p<0.05, **p<0.01

Results

KVA12123 Fc modification increases binding to FcRn and decreases binding to FcγRI, FcγRIIA, FcγRIIIA.



Antibody	EC50 FcRn (ug/mL)	EC50 FcRn (nM)
KVA12123 (YTE, IgG1)	0.142	0.95
KVA12104 (WT, IgG1)	0.750	5.0

Figure 3. Inhibition of human IgG binding to Fc receptors by anti-VISTA antibodies was measured using AlphaLisa binding kits. Biotinylated Fc receptors were mixed with anti-VISTA antibodies, human IgG acceptor beads, and streptavidin donor beads and then incubated for 90 minutes at room temperature. Signal was measured at 680nm/615nm (excitation/emission).

KVA12123 Fc modification extends serum exposure

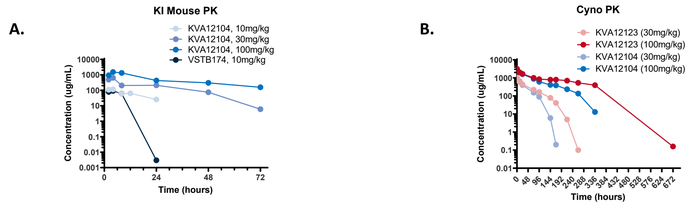


Figure 4. PK studies with (A) mice and (B) cynomolgus monkeys were conducted. Human VISTA KI mice or female cynomolgus monkeys were administered a single IP (mouse) or IV (cyno) dose of either 10mg/kg, 30mg/kg or 100mg/kg of anti-VISTA antibodies. Serum was sampled over time and analyzed by ELISA to determine serum exposure of anti-VISTA antibodies. Mean exposure values over time were graphed (n=2 mice and n=1 monkey, per group).

❖ KVA12123 shows at least 2-fold lower Antibody-dependent cellular cytotoxicity (ADCC) activity when compared to VSTB174, with no detectable (complement-dependent cytotoxicity) CDC

KVA12123 does not induce Cytokine Release Syndrome (CRS) in human whole blood

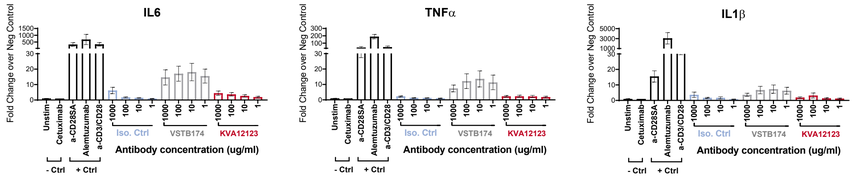


Figure 5. A Cytokine Release Assay (CRA) was conducted using whole blood from 11 healthy human male and female donors was incubated in the presence of KVA12123 or control antibodies for 24 hours. Secretion of IL-6, TNFα, and IL1β were quantified using a Luminex MAGPIX cytokine panel assay. Data was normalized to the CRS assay negative controls and the average values were plotted (n=11). Error bars represent SEM.

KVA12123 is well-tolerated in non-human primate toxicology studies

Study Endpoints	Results
Clinical observations	✓ No mortality
PK evaluation	✓ No overt clinical signs or weight loss
Hematology	✓ No treatment related findings for clinical pathology endpoints
Clinical Chemistry	✓ Well tolerated
Immunogenicity	✓ **No change of CRS cytokine levels**
	✓ **Extended PK**

Cytokine analysis was carried out in a repeat-dose GLP non-human primate study. No changes in CRS-linked cytokine levels were noted for **IL-6**, IL-1β, IL-2, IL-4, IL-5, IL-10, IL-12/23 (p40), IL-13, IL-17A, IFN-γ, TNF-α, MIP-1β, or G-CSF and only slight, non-adverse test article related changes were seen in IL-1ra, MCP-1, and **IP-10**.

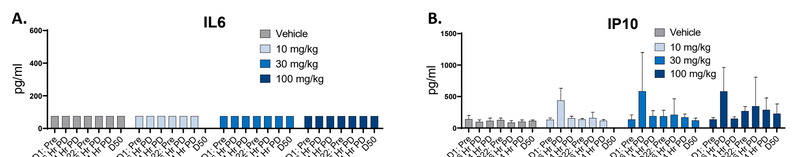


Figure 6. Toxicology study shows no cytokine release (A) IL-6 and a slight cytokine release (B) IP-10 . 36 cynomolgus monkeys (18 males and 18 females) were dosed with KVA12123 or the vehicle control at 0, 10, 30, and 100 mg/kg via intravenous (IV) injection once weekly for 4 weeks. Blood was collected on Days 1 and 22: predose (pre), 6 and 24 hours (hr) postdose (PD).

❖ **KVA12123 has demonstrated potent single-agent anti-tumor activity and a favorable safety profile. KVA12123 is being taken forward for clinical development.**

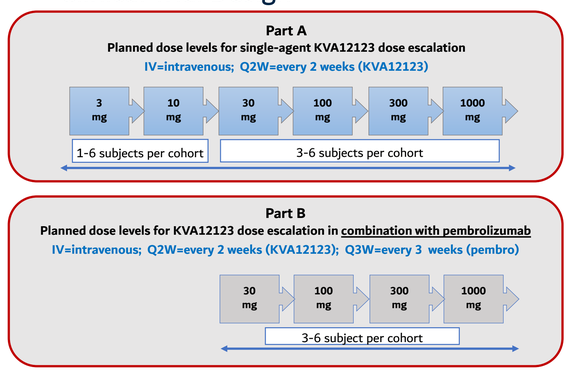
Clinical Trial Design

Patient population
- Patients with advanced solid tumors

Primary objectives
- Safety and tolerability
- Recommended Phase 2 dose (RP2D) or maximum tolerated dose (MTD) of KVA12123

Secondary objectives
- Pharmacokinetics
- Immunogenicity
- Tumor response in subjects with advanced solid tumors per iRECIST (objective response rate ;ORR & progression-free survival;PFS)

Exploratory objectives
- Receptor Occupancy
- Biomarkers



Conclusions

- KVA12123 has been selected as our clinical lead
- KVA12123 has an extended PK and binds to a unique epitope
- KVA12123 induces a strong anti-tumor response as a single agent or in combo therapies with anti-PD1 in multiple tumor models
- KVA12123 is well tolerated and has been shown not to induce release of CRS cytokines in non-human primate studies or in human whole blood.
- Clinical trial to start December 2022