KVA 12.1 a novel fully human anti-VISTA antibody to treat cancer patients with advanced solid tumors

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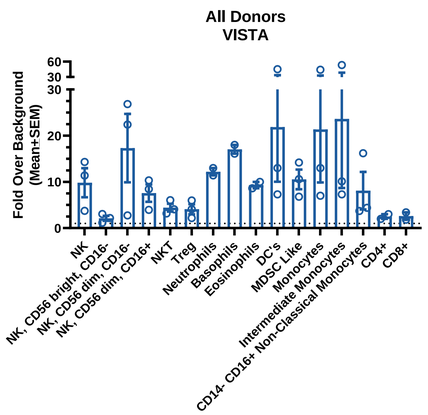
Background

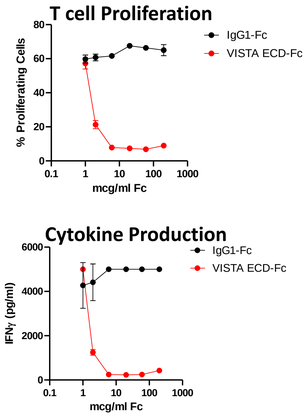
- VISTA (V-domain Ig Suppressor of T cell Activation) is a unique CD28/B7 family member with poorly defined receptors. However, VISTA itself, PSGL-1, VSIG3, VSIG8 and LRIG1 have been suggested as putative receptors.
- VISTA is highly expressed on circulating and intratumoral myeloid cells especially MDSCs.
- VISTA is a negative regulator that directly 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.

VISTA expression on Human whole blood

Representative of 3 healthy donors: Donor # 4903 shown



VISTA has profound negative regulatory effect on T Cell activation and proliferation

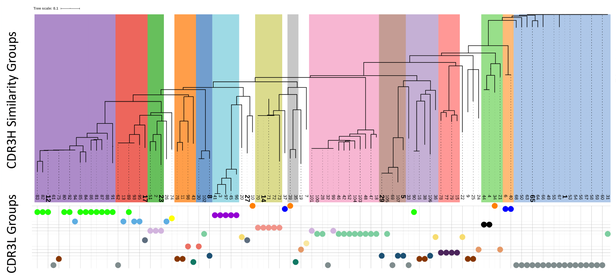


Objectives

- Select a lead clinical candidate against VISTA –> KVA12.1
- Develop a clinical plan for patients with advanced solid tumors

Results

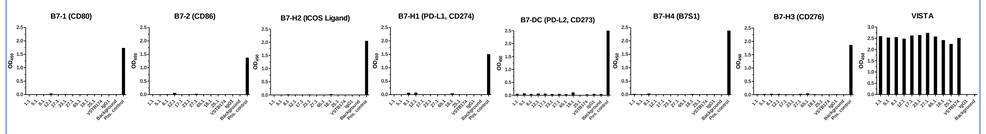
Exceptional antibody diversity in both Heavy and Light Chains



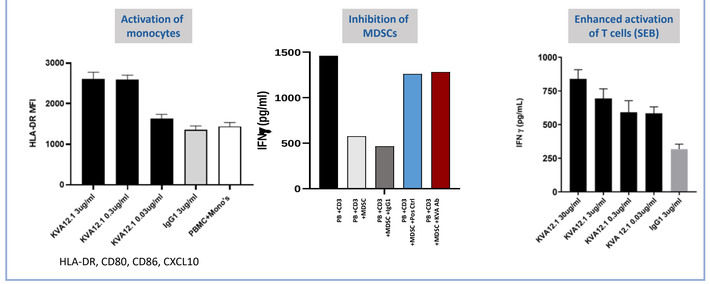
107 fully human ScFv antibodies directed against Human VISTA were generated

- 15 V_H diversity groups
- 15 V_L diversity groups
- Highest diversity in CDR3H

KVA antibodies bind only to VISTA and not other B7 family proteins

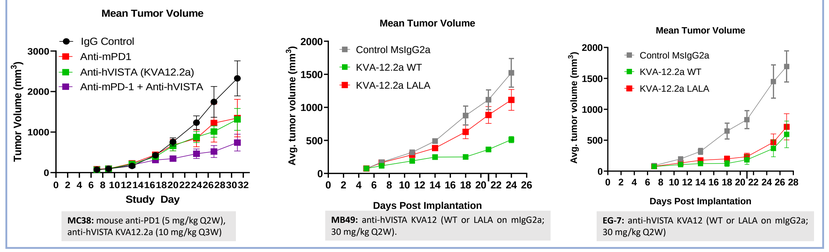


Mechanism of action of our lead anti-VISTA antibody : KVA12.1



HLA-DR, CD80, CD86, CXCL10

KVA12 antibody induces strong anti-tumor response as a single agent or in combo-therapies



MC38: mouse anti-PD1 (5 mg/kg Q2W), anti-hVISTA KVA12.2a (10 mg/kg Q3W)

MB49: anti-hVISTA KVA12 (WT or LALA on mIgG2a; 30 mg/kg Q2W).

EG-7: anti-hVISTA KVA12 (WT or LALA on mIgG2a; 30 mg/kg Q2W)

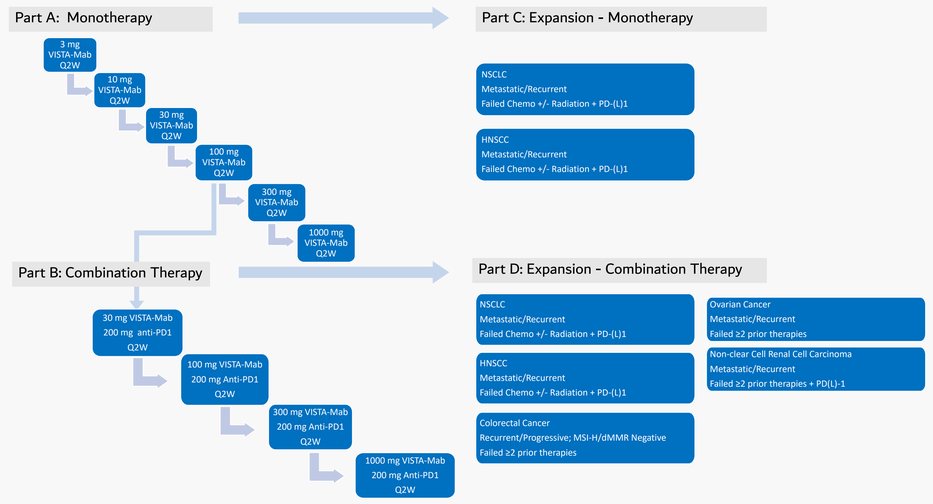
Safety: KVA12.1 is well-tolerated in NHP toxicology studies

Studies	Purpose	Endpoints	Results
CRL #1832-032	PK and Tolerability	Clinical observations PK evaluation Hematology Clinical Chemistry Immunogenicity	✓ No mortality ✓ No overt clinical signs or weight loss ✓ No treatment-related findings for clinical pathology endpoints ✓ No change of CRS cytokine levels ✓ Exceptional tolerability ✓ Extended PK
CRL #1832-033	PK and Tolerability		
CRL #1832-034	PK and Tolerability		
CRL #1832-035	PK and Tolerability		
CRL #2032-4535	Non-GLP Toxicology 4-weeks Dose Range Finding		
CRL #2032-4536	GLP Toxicology 28-Days Repeat Dose – 4-weeks recovery		

Clinical Development Plan

Clinical Protocol Design

Phase 1/2 trial is proposed as follows:



Study Endpoints

- **Clinical**
  - Safety measurements and DLTs as single agent and in combination with anti-PD1
  - Overall Response Rate and durability of response using RECISTv1.1
  - Determined MTD and R2PD
- **Pharmacologic and Biomarker**
  - PK
  - Receptor Occupancy
  - Cytokine and Chemokine profiles in plasma samples
  - Flow Cytometry for PD marker on Immune cells
  - Tumor biopsies : multiparameter analysis to evaluate tumor cells as well as Immune infiltrating cells. Characterized expression of immune checkpoint and exhausted markers.

Conclusion

- **107 fully human ScFv anti-VISTA antibodies were generated and analyzed**
- **KVA12.1 was selected as our clinical lead**
- **KVA12.1 has an extended PK and a unique epitope**
- **KVA12.1 induces strong anti-tumor response as a single agent or in combo-therapies with anti-PD1 in multiple tumor models**
- **KVA12.1 is safe and does not exhibit any sign of Cytokine Release Syndrome in NHP as well as human whole blood**
- **Clinical Trial will start end of 2022**