# KVA 12.1 a novel fully human anti-VISTA antibody clinical trial design in monotherapy and in combination with an anti-PD1 antibody. #268

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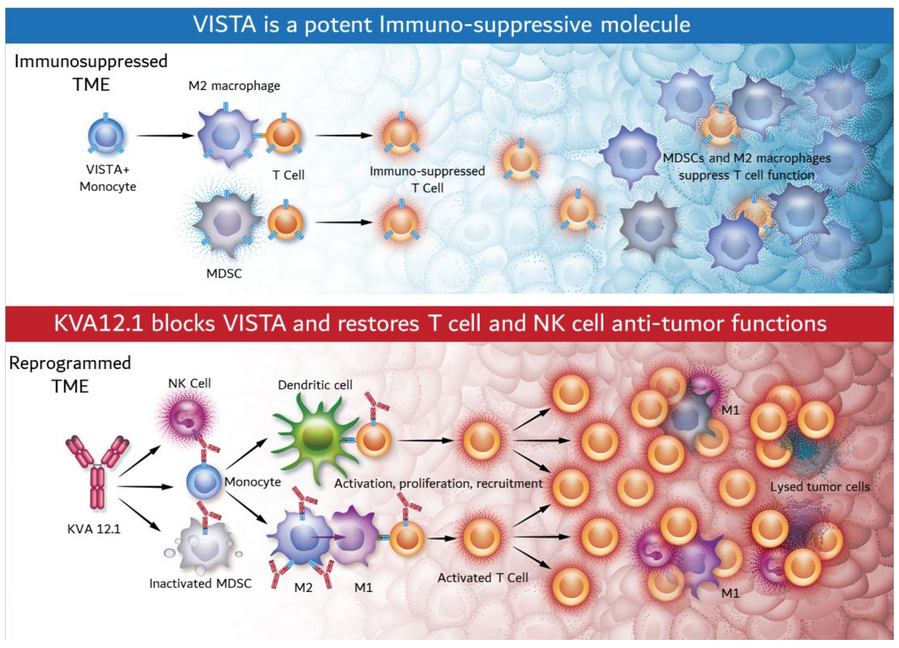
## Background

- V-domain Ig Suppressor of T cell Activation (VISTA) is an immune-suppressive checkpoint inhibitor of T cell response expressed in the immuno-suppressive tumor microenvironment.
- An increase in VISTA expression has been described after treatment with anti-CTLA-4 or anti-PD1-(L)1.
- VISTA blockade with KVA12.1, a fully human anti-VISTA antibody developed by Kineta Inc., restores an efficient antitumor immune response in different tumor models as a single agent or in combination with anti-PD1 or CTLA-4.
- KVA12.1 exhibits high potency and binds to a unique epitope.
- KVA12.1 was well-tolerated in toxicology studies in cynomolgus monkey, where hematology and clinical chemistry evaluations as well as clinical observations revealed no indicators of toxicity.
- Cytokine levels associated with CRS (e.g., TNF-α, IL-6, IL-1β) were assessed, and none were elevated.
- KVA12.1 exhibits a long half-life consistent with other monoclonal antibody checkpoint inhibitors.




## Objectives

A Phase 1/2 multicenter, open label, dose escalation and dose expansion study of intravenous infusion of KVA12.1 as a monotherapy and in combination with a fixed dose of an anti-PD1 antibody in patients with advanced refractory or metastatic solid tumors.

**Primary objective**: Evaluate the safety, tolerability, Dose Limiting Toxicity (DLT), Maximum Tolerated Dose (MTD) and Identify the Recommended Phase 2 Dose (RP2D) of VISTA-Mab when administered alone and in combination with an anti-PD1 antibody.

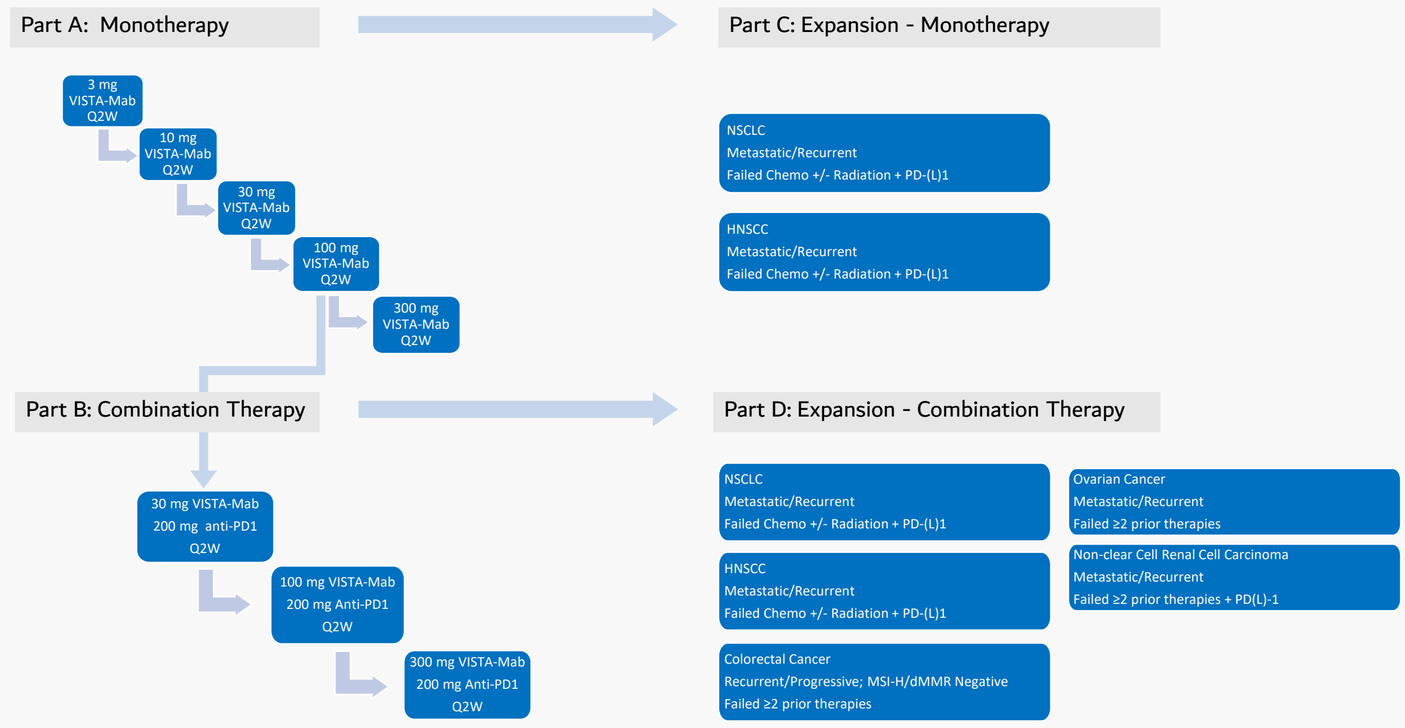
**Secondary objectives**: Investigate i) the PK of VISTA-Mab; ii) VISTA-Receptor Occupancy; iii) the anti-tumor activity of VISTA-Mab (alone and in combination); iv) the immunogenicity of VISTA-Mab (alone or in combination).

## Clinical Development Plan

### Clinical Protocol Design

Phase 1/2 trial is proposed as follows:

- **Part A:** Ascending dose of KVA12.1 in Monotherapy (Subject numbers determined using Bayesian Optimal Interval Design (BOIN))
- **Part B:** Ascending dose of KVA12.1 in Combination with a fixed dose of anti-PD1 (Subject numbers determined using BOIN)
- **Part C:** Expansion Cohort of KVA12.1 in Monotherapy (Subject numbers determined using Simon 2-stage design)
- **Part D:** Expansion Cohort of KVA12.1 in Combination with Anti-PD1 (Subject numbers determined using Simon 2-stage design)

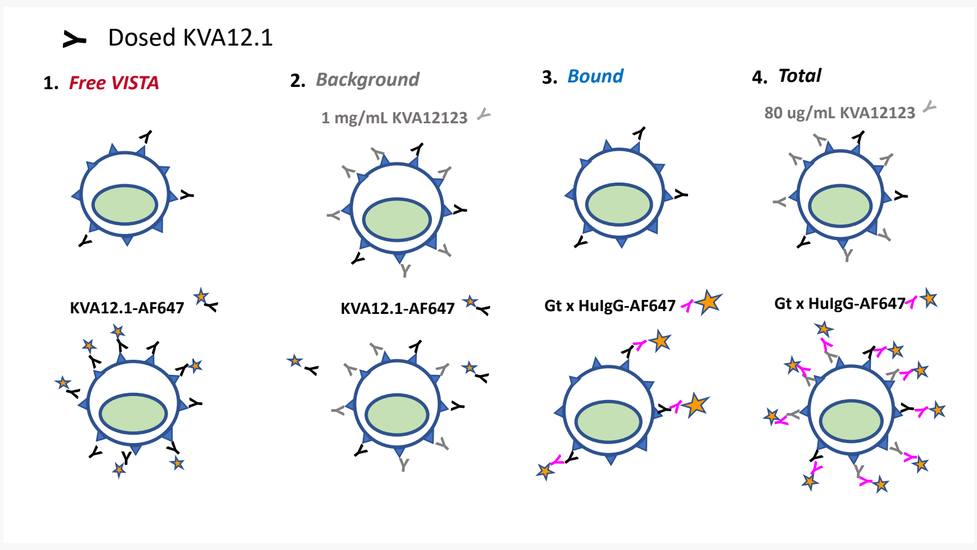



### Study Endpoints

➢ **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.

Methods:
- $K_2$ EDTA whole NHP blood samples were collected, diluted in 10% cold DMSO, frozen, and stored in $LN_2$ until the day of assay.
- Samples were acquired the same day and analyzed using FlowJo.
- Cells were gated for Singlets, and Viability. Viable CD45+ cells were further gated on CD14+, HLA-DR+ cells.
- CD14+, HLA-DR+ cells were subsequently analyzed for Alexa Fluor647 Median Fluorescence Intensity.




Normalized % Free, normalized % Bound, and Weighted % RO were calculated.

a. Normalized % Free=(Free-Bkgd)/(Free-$Bkgd_{p-d}$). RO=100-% Free.
b. Normalize % Bound=100 x (Bound-$Bound_{p-d}$)/(Total-$Bound_{p-d}$) = % RO
c. Weighted % RO=100 x (100-% Free)/((100-% Free) + (100-% Bound))

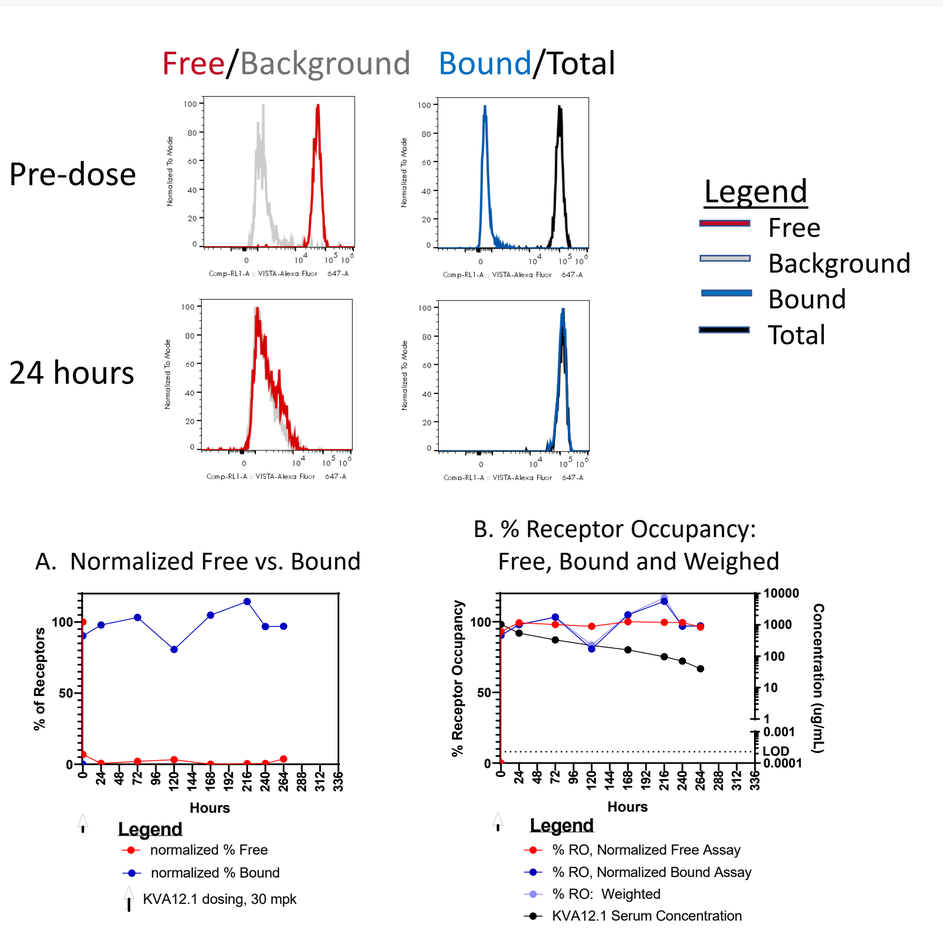



Figure: CD14+, HLA-DR+ monocytes of KVA12.1-dosed NHP subject were analyzed as described in Methods above. Free receptors were nearly undetectable, and Bound receptor staining was approximately equal to Total receptor staining throughout 11 days post-dose (A). A high degree of agreement was observed between the RO measured by the normalized Free and normalized Bound assays (B). The Weighted % RO demonstrates 100% occupancy throughout the 11 days post-dose (B). PK analysis of KVA12.1 serum concentrations is represented for comparison in black.

## Conclusion

Chemistry, manufacturing and controls and toxicology studies are currently on-going,
We expect the beginning of our clinical trial in solid tumors in mid-2022.