VISTA-101: A phase 1/2 clinical trial of KVA12123, an engineered IgG1 targeting VISTA alone and in combination with pembrolizumab in advanced solid tumors

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Background

VISTA (V-domain Ig suppressor of T cell activation) is a strong driver of immunosuppression in the tumor microenvironment (TME)

- A negative immune checkpoint that suppresses T cell function in a variety of solid tumors
- Highly expressed in cold tumors and correlates with poor outcomes in cancer patients
- Up-regulated after checkpoint inhibitor therapy and associated with treatment failure
- Blocking VISTA induces a polyfunctional immune response that addresses immunosuppression and drives anti-tumor responses

KVA12123 is a VISTA blocking immunotherapy in development as a twice weekly infusion

- An engineered IgG1 mAb that binds to a unique epitope at acidic and neutral pHs
- Induces a strong anti-tumor response as a single agent and in combination with anti-PD1 in multiple preclinical tumor models
- Well tolerated and does not induce the release of CRS associated cytokines in non-human primates or in human whole blood
- May be an effective immunotherapy for many types of cancer including NSCLC, colorectal (CRC), renal cell carcinoma (RCC), head and neck (SCCHN), and ovarian (OC) cancers

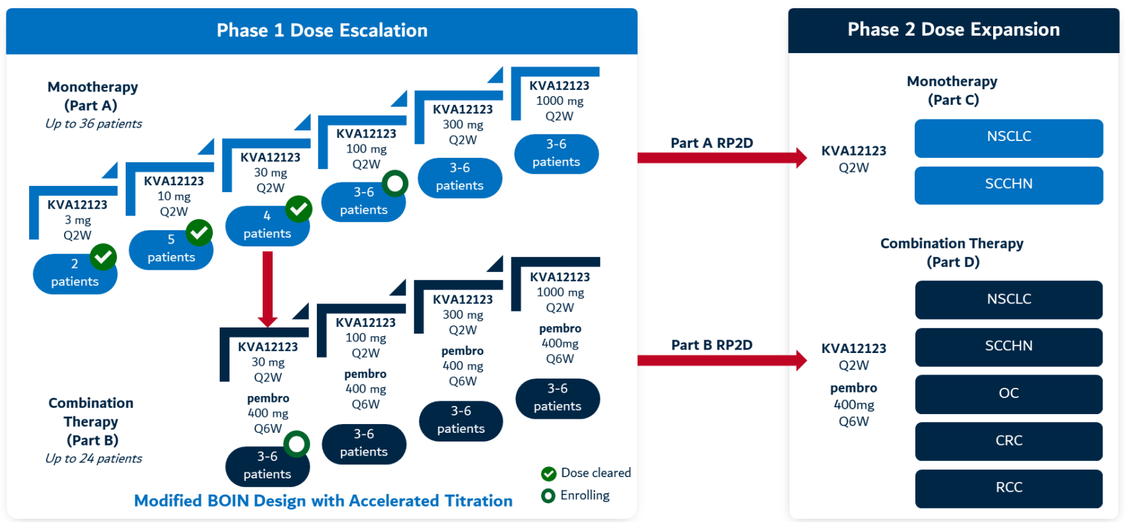
VISTA-101 study objectives

VISTA-101: Phase 1/2 open-label clinical trial of KVA12123 alone and in combination with pembrolizumab in patients with advanced solid tumors (NCT05708950)

- **Primary**: safety and tolerability, recommended Phase 2 dose (RP2D) or maximum tolerated dose (MTD) of KVA12123
- **Secondary**: pharmacokinetics, immunogenicity, tumor response in subjects with advanced solid tumors per iRECIST (ORR)
- **Exploratory**: biomarker and receptor occupancy

VISTA-101 study design

Cleared initial monotherapy cohorts and started combination cohort with pembrolizumab



The study was approved by the WCG Institutional Review Board (IRB)-approved protocol No. 20230297 and by the University of California, Los Angeles (UCLA) IRB-approved protocol No. IRB#22-002003. The patients provided written informed consent to participate in this study.

Patient demographics & characteristics

Demographics

Characteristic	Statistic	Result
Gender N (%)	Male	7 (64)
	Female	4 (36)
Race/Ethnicity N (%)	White	7 (64)
	Black or African American	2 (18)
	Hispanic or Latino	1 (9)
	Other/Not specified	1 (9)
Age Mean (Range)	Years	60.8 (47-72)

Stage and prior treatments

Characteristic	Statistic	Result
Stage at Initial Diagnosis N (%)	I	1 (9)
	II	2 (18)
	III	0 (0)
	IV	6 (55)
	Not reported	2 (18)
Prior treatment N (%)	Radiation	9 (82)
	Antineoplastic medication	11 (100)
	Antineoplastic surgery	11 (100)
Baseline ECOG N (%)	Grade 0	2 (18)
	Grade 1	9 (82)

KVA12123 monotherapy safety

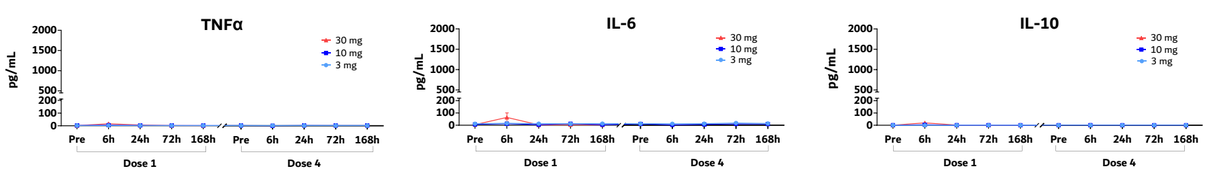
KVA12123 was well tolerated in 3, 10 & 30 mg monotherapy cohorts

- No dose limiting toxicities (DLT) were observed
- All KVA12123 treatment emergent adverse events (TEAE) were grades 1-2

MedDRA Preferred Term	3mg N=2 (%)	10mg N=5 (%)	30mg N=4 (%)	All doses N=11 (%)
Total Subjects With Any Related TEAE	**1 (50)**	**3 (60)**	**1 (25)**	**5 (45)**
Infusion related reaction	0 (0)	2 (40)	1 (25)	3 (27)
Constipation	1 (50)	0 (0)	0 (0)	1 (9)
Diarrhoea	0 (0)	1 (20)	0 (0)	1 (9)
Dyspepsia	1 (50)	0 (0)	0 (0)	1 (9)
Arthralgia	0 (0)	1 (20)	0 (0)	1 (9)
Myalgia	1 (50)	0 (0)	0 (0)	1 (9)
Tachycardia	0 (0)	1 (20)	0 (0)	1 (9)
Blood potassium decreased	1 (50)	0 (0)	0 (0)	1 (9)
Decreased appetite	0 (0)	1 (20)	0 (0)	1 (9)
Cough	0 (0)	0 (0)	1 (25)	1 (9)
Rash maculo-papular	0 (0)	1 (20)	0 (0)	1 (9)

No evidence of CRS-associated cytokine induction after KVA12123 administration

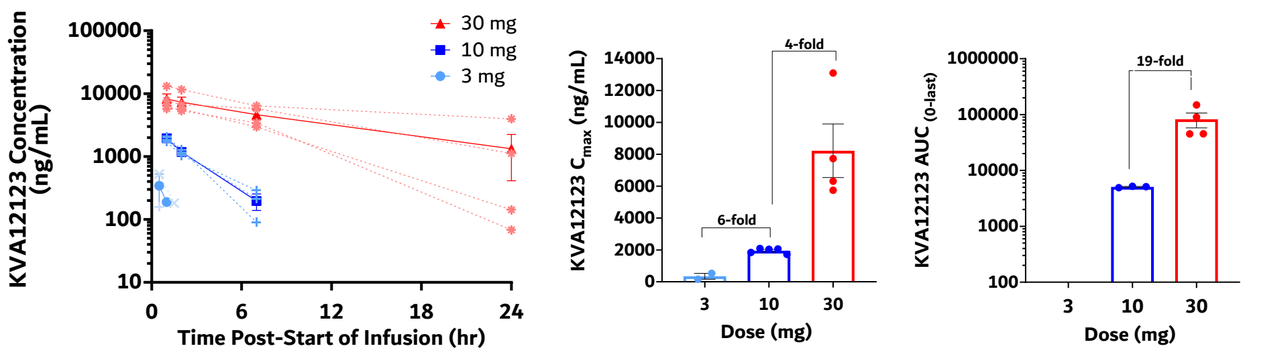
TNFα, IL-6 & IL-10 are key drivers of CRS



The cytokine serum concentrations pre- and post-infusion of KVA12123 after the first and the 4th dose analyzed from 11 patients. The samples were processed using MSD V-PLEX Plus cytokine and chemokine kits according to the manufacturer's instructions.

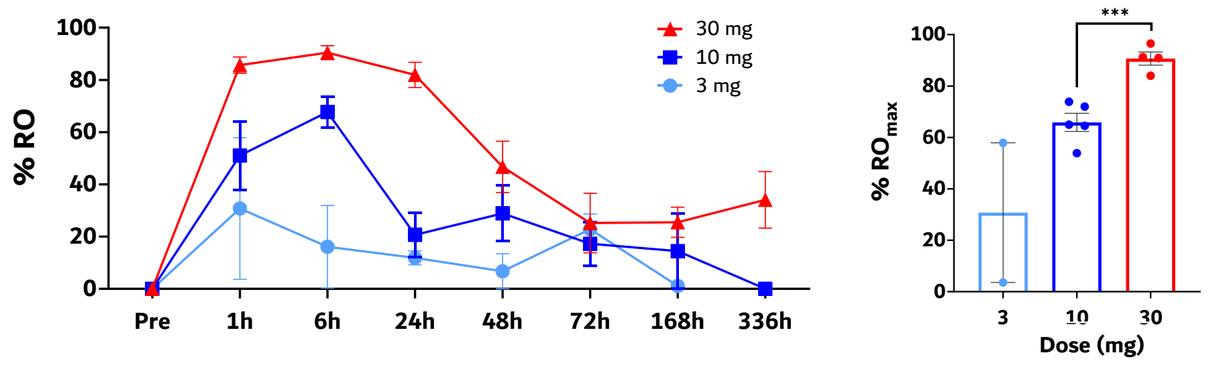
Pharmacokinetics and VISTA receptor occupancy (RO)

KVA12123 exhibited a greater than dose-proportional pharmacokinetic profile



Pharmacokinetic profiles obtained from 11 patients after a single administration of KVA12123. The following parameters are presented: C_{max} (maximum observed concentration) and AUC_{0-t} (area under the concentration-time curve from time 0 to the timepoint with the last measurable concentration).

KVA12123 achieved >90% VISTA receptor occupancy across patients in the 30 mg dosing cohort



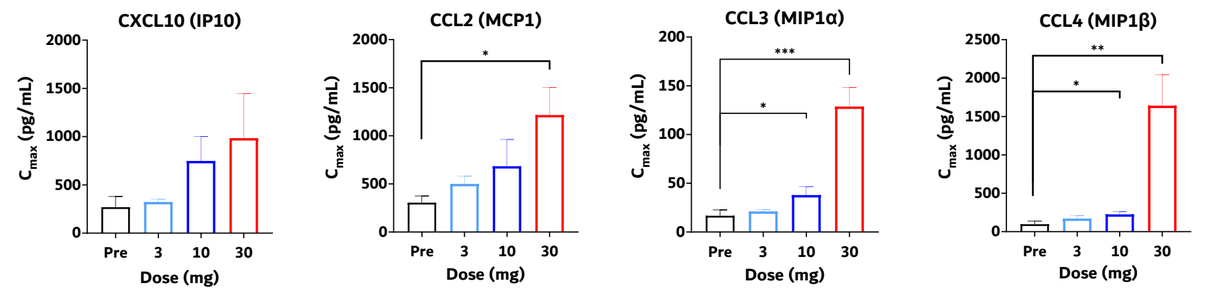
The VISTA-receptor occupancy on circulating monocytes in 11 patients after a single administration of KVA12123. Kineta utilized a proprietary method to evaluate VISTA receptor occupancy. *** p<0.001

Biomarkers

KVA12123 demonstrated dose proportional induction of pro-inflammatory biomarkers and on-target immune cell responses involved in anti-tumor activity

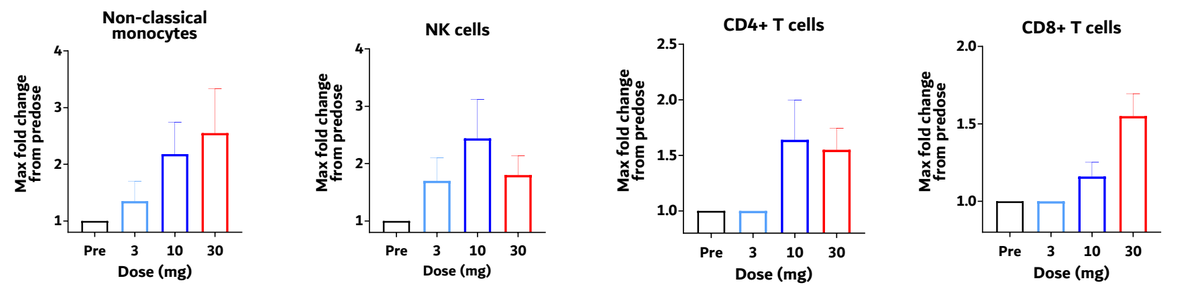
- Induces pro-inflammatory myeloid derived cytokines/chemokines involved in immune cell activation and recruitment in the tumor microenvironment
- Increases anti-tumor Non-classical monocytes and NK cells in peripheral blood
- Increases helper ($CD4^+$) and cytotoxic ($CD8^+$) T cells in the blood

Cytokines/Chemokines



The cytokine serum concentrations pre- and post-infusion of KVA12123 from 11 patients. The samples were processed using MSD V-PLEX Plus cytokine and chemokine kits according to the manufacturer's instructions. * p<0.05, ** p<0.01, *** p<0.001

Immunophenotyping



Changes of peripheral blood immune cell subpopulations after the first administration of KVA12123. Flow cytometric data acquisition and analysis were performed using the FACSCantoII™ flow cytometer. Data was acquired and analyzed using BD FACSDiva™ software. Fold change from pre-dose was calculated for each sub-population (expressed as % CD45+).

Tumor type and best overall response (BOR)

Cohort	Patient	Tumor Type	BOR
3 mg	100-002	Bladder	SD
	101-001	Leiomyosarcoma	SD
10 mg	100-003	Colon	SD
	101-002	Pancreatic	NE
	104-003	Urothelial	NE
	105-001	Renal cell	SD
	109-001	Carcinosarcoma to lung	SD
30 mg	100-004	Non-small cell lung cancer	SD
	101-003	Pancreatic	PD
	101-004	Pancreatic	NE
	105-002	Urothelial	PD

Stable Disease (SD) **Progressive Disease (PD)** **Not Evaluable (NE)**

- Diverse tumor types enrolled in VISTA-101 clinical trial
- Additional monotherapy safety and efficacy data anticipated in Q2 2024

Conclusions

- VISTA is a promising innate immune drug target that is nonredundant with T cell focused therapies
- Cleared first three KVA12123 monotherapy cohorts (3, 10, 30 mg) with 11 patients dosed
- Clinical safety profile established as KVA12123 was well tolerated and no DLTs were observed
- No evidence of CRS-associated cytokines (IL-6, TNFα & IL-10) were detected
- KVA12123 exhibited a greater than dose-proportional pharmacokinetic profile
- Achieved >90% VISTA RO across patients in the 30 mg dosing cohort approaching an optimal clinical dose
- Demonstrated efficacy-related cytokine secretion of CXCL10, MCP1, MIP1α & MIP1β
- On target changes in anti-tumor immune cell subpopulations were observed after treatment
- VISTA-101 trial is advancing to higher monotherapy dose levels and in combination with pembrolizumab
- Additional monotherapy data and combination therapy clinical data anticipated in Q2 2024