# Phase 1 Study of CI-8993 anti-VISTA antibody in patients with advanced solid tumor malignancies

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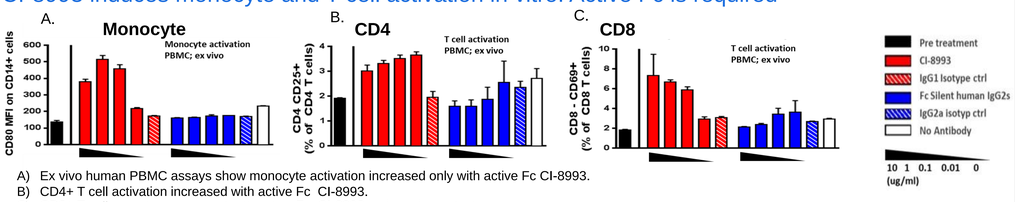
## Background

VISTA (V-domain Ig suppressor of T cell activation) is a key negative immune checkpoint regulator, locking T cells in a quiescent state, unlike PD1 and CTLA4, which are expressed on activated T cells [1]. As resistance develops to PD-1 and CTLA-4 directed therapy, VISTA expression is greatly increased, forcing cells into a quiescent state [2]. VISTA is also expressed at high levels on the surface of myeloid cells within the stromal compartment of myeloid-rich solid tumors, such as lung cancer. Pre-clinically, anti-VISTA monoclonal antibody treatment increased the number of tumor-specific T cells in the periphery, enhanced the infiltration, proliferation and effector function of tumor-reactive T cells within the tumor microenvironment (TME). VISTA blockade alters the suppressive feature of the TME by decreasing the presence of monocytic myeloid-derived suppressor cells (MDSC) and increasing the presence of activated dendritic cells (DCs) within the TME leading to enhanced T cell mediated immunity.

## CI-8993: Pre-clinical Rationale

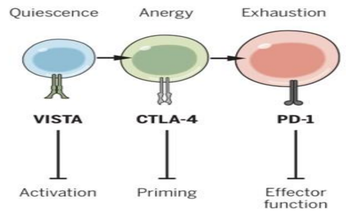
CI-8993 is a first-in-class, fully human immunoglobulin (Ig) G1κ monoclonal antibody (mAb) against the VISTA ligand.

### CI-8993 induces monocyte and T cell activation in vitro: Active Fc is required




A) Ex vivo human PBMC assays show monocyte activation increased only with active Fc CI-8993.
B) CD4+ T cell activation increased with active Fc CI-8993.
C) CD8+ T cell activation increased with active Fc CI-8993 in dose dependent manner.

**Integration of VISTA with other well-established negative checkpoint regulators of T cell activation**

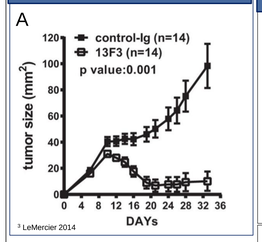



**VISTA is the only oncology check point on <u>resting</u> T cells; therefore affects earliest phase of response to tumor antigen:**

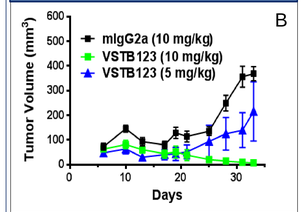
- It is the key regulator of quiescence (vs CTLA4 regulates priming and PD1 regulates effector function).
- T-Cells stuck in quiescent state cannot be acted upon by anti-CTLA4 or PD1 antibodies.
- As resistance develops to PD-1 and CTLA-4 directed therapy, VISTA expression is greatly increased, forcing T-cells into a quiescent state.

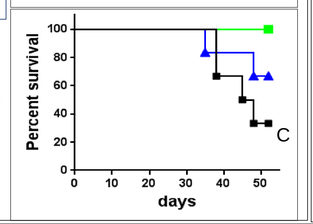
### Anti-Cancer Activity After Blocking VISTA in Preclinical Models

**B16ova melanoma model**




**MB49 bladder carcinoma model**

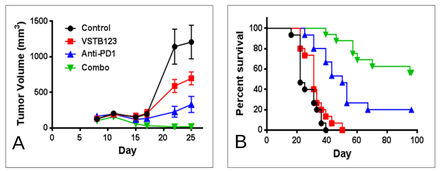


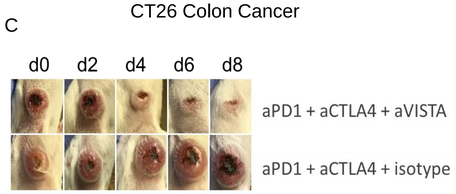

Murine anti-VISTA antibodies are highly active in orthotopic tumor models and overcome anti-PD1 and anti-CTLA4 resistance.

### Synergy with other checkpoint inhibitors

Murine MB49 Bladder Carcinoma

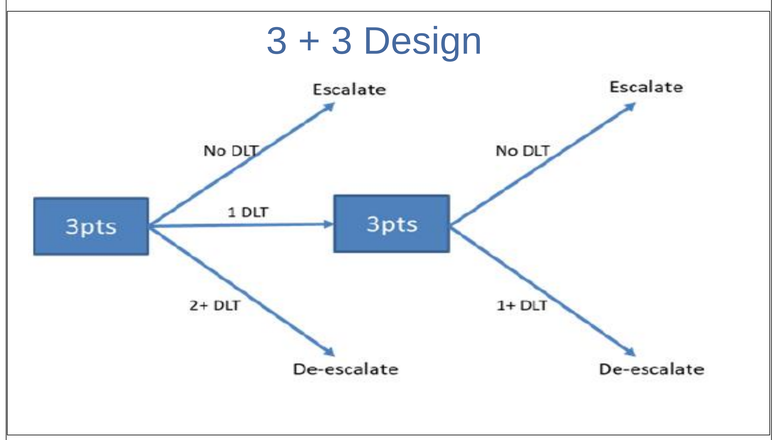



CT26 Colon Cancer




## Methods and Study Design (NCT04475523)

Phase 1, open-label, dose-escalation study conducted at multiple sites in the United States over 36 months starting at 0.15mg/kg. This dose of CI-8993 demonstrated target-related clinical findings and pharmacodynamic activity in prior human clinical evaluation.




The dose escalation process has a 3+3 design. Patients with solid tumor malignancy (non-lymphoma) that is metastatic or unresectable and considered relapsed and/or refractory to prior therapy will be included. It is expected that approximately 50 patients evaluable for DLTs may be required to fill enough dose cohorts to establish the initial recommended phase 2 dose (RP2D). Patients will be treated with initial step-dose(s) of CI-8993 by IV infusion for increased safety. This will be followed by full doses until disease progression or toxicity.

### Objectives

- Primary:
  - To identify a safe and tolerable RP2D of CI-8993 for administration to patients with relapsed/refractory solid malignancies and characterize dose-limiting toxicities (DLTs) and the maximum tolerated dose (MTD) of CI-8993 in this population.
- Secondary:
  - To assess the pharmacokinetics (PK), pharmacodynamics (PD), anti-drug antibodies (ADA), and therapeutic intent as measured using tumor imaging of anti-cancer activity of CI-8993.
- Exploratory:
  - Analysis of tumor tissue for factors that may predict anticancer efficacy, which may include, but are not limited to:
    - Expression of VISTA, CD3, CD4, CD8, forkhead box P3, CD68, β2-microglobulin, HLA-A, B, C, MHC class II, and PD-L1 by immunohistochemistry (IHC) staining.
    - Frequency of monocytic and granulocytic myeloid derived suppressor cells (MDSCs).
    - T cell-inflamed microenvironment.
    - Tumor mutational burden, fragment crystallizable receptors (FcRs), alleles, and microsatellite instability.
  - PK parameters that may be surrogates of safety or efficacy.
  - Ex vivo assessment of potentiation of extracellular and intracellular cytokine production.

## Major Eligibility Criteria

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| ≥ 18 years of age | HIV, hepatitis B, untreated hepatitis C or uncontrolled intercurrent medical illness |
| Relapsed/refractory solid tumor (non-lymphoma) | > 10 mg/day of prednisone equivalent or autoimmune disease with flair in last 6 months requiring an immunosuppressant |
| Metastatic or unresectable | CNS disorder: CNS malignancy/metastasis, stroke, TIA, seizure disorder |
| Evaluable disease | Personal or family history of HLH or MAS |
| Archival FFPE tumor tissue (core biopsy) | Prior CAR-T therapy or Allogenic organ or bone marrow transplant (BMT) |
| (ECOG) performance status: 0 - 1 | RT or other anticancer therapy < 2 wks. or immunotherapy < 3 wks. of 1st CI-8993 dose |
| Adequate organ and bone marrow function | Immune-related AE with prior immunotherapy that was Grade 3 or higher |
| Stable venous access | Therapeutic anti-coagulation |

FFPE: formalin-fixed, paraffin-embedded, ECOG: Eastern Cooperative Oncology Group, CNS: central nervous system, TIA: transient ischemic attack, HLH: hemophagocytic lymphohistiocytosis, MAS: macrophage activation syndrome, CAR-T: chimeric antigen receptor T cell, RT: radiation therapy, AE: adverse event.

## Safety Measures

As with any new product, administration of CI-8993 may involve risks that are currently unforeseen. Subjects enrolled in clinical studies with CI-8993 must meet baseline hematologic eligibility criteria as defined by the study protocol. Subjects will be monitored routinely for signs of local or systemic infection or bleeding. Hematologic status (complete blood counts) will be evaluated for toxicity, at a minimum, prior to each dose administration and additionally throughout treatment as clinically indicated. Cytokine release syndrome (CRS) is a known risk of immunological compounds, has been designated as an adverse event (AE) of special interest and grouped together with infusion-related reactions (IRRs) as treatment-emergent AE and will be closely monitored in this study. In addition to administration of a desensitizing step-dose of CI-8993 intended to mitigate CRS and CRS-related CNS toxicity, the protocol includes a comprehensive safety plan of pre- and post-infusion medication for the mitigation of AEs.

## Conclusions and Future Directions

- Preclinically, CI-8993 shows anti-tumor efficacy and synergy with other checkpoint inhibitors (CPIs) through TME modulation via increased peripheral tumor-specific T cells numbers, monocyte- and T cell activation.
- This may prevent or overcome adaptive VISTA-related resistance to CPIs.
- CI-8993 is the first monoclonal antibody targeting VISTA to be tested in human solid tumor patients. *NCT04475523* is currently recruiting patients.

## References

1. ElTanbouly MA, Noelle RJ et al. VISTA is a checkpoint regulator for naïve T cell quiescence and peripheral tolerance. Science. 2020 Jan 17;367(6475):eaay0524. doi: 10.1126/science.aay0524. PMID: 31949051; PMCID: PMC7391053.
2. Gao J, Ward JF, Pettaway CA, et al. VISTA is an inhibitory immune checkpoint that is increased after ipilimumab therapy in patients with prostate cancer. Nat Med 2017; 23(5):551-55.
3. Le Mercier I, Wang L et al. VISTA Regulates the Development of Protective Antitumor Immunity. Cancer Res. 2014 Apr 1;74(7):1933-44. doi: 10.1158/0008-5472.CAN-13-1506. PMID: 24691994; PMCID: PMC4116689.

## Further Information

**ClinicalTrials.gov identifier: NCT04475523**

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