#761: Pharmacokinetic and Pharmacodynamic data from a Phase 1 Study of CI-8993 Anti-VISTA Antibody in Patients with Advanced Solid Tumors

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Background

- V-set immunoglobulin domain suppressor of T cell activation (VISTA) is a novel immunoregulatory protein that is broadly expressed on cells of the myeloid and lymphoid lineages, and is frequently implicated as a poor prognostic indicator in multiple cancers (1)
- VISTA is the only oncology checkpoint on quiescent T cells affecting earliest phase of response to tumor antigen (1)
- Negative immune checkpoint regulation by VISTA has been described as a mechanism of resistance in melanoma and prostate patients treated with anti- CTLA 4 and anti-PD-1/PD-L1 inhibitors (2,3)
- 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 (4)

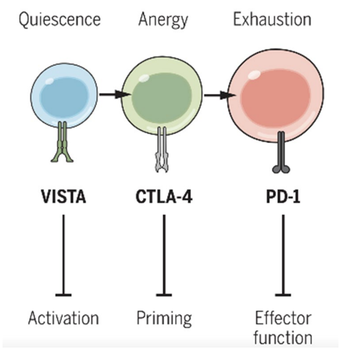
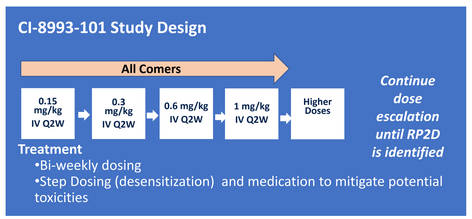


Figure 1: Integration of VISTA with other well established negative checkpoint regulators of T cell activation (1)

CI-8993-101 Study Design (NCT04475523)

- CI-8993-101 is an open label phase 1 dose escalation study with 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, were included for this study
- Patients were enrolled into cohorts structured to receive step-dosing regimen before administering a single full dose of CI-8993 (Table1). The full doses ranged from 0.15 mg/kg to 0.6mg/kg over three different cohorts



Cohort	Step Dose 1 (mg/kg)	Step Dose 2* (mg/kg)	Full Dose (mg/kg)
1	0.05	0.05	0.15
2	0.05	0.05	0.30
3	0.05	0.15	0.6
4**	0.05	0.15	1.0
5**	0.05	0.15	2.0
6**	0.05	0.15	4.0

* Step dose 2 taken 72 hours after step dose 1.
** Initial step dose administered within 1 week prior to full dose.

Table 1: CI-8993-101 Step and Full Dosing Schema

Methods

- Immune related PD, cytokine quantification and immune phenotyping was performed on peripheral blood from patients receiving a single full dose of CI-8993, divided in 3 cohorts (0.15, 0.3 and 0.6 mg/kg)
- Plasma concentration of CI-8993 (PK) was quantified on samples from patients at time points following step-dose, and a single full dose administration of CI-8993

Abbreviations
Pharmacokinetic (PK), Pharmacodynamic (PD), Dose Limiting Toxicities (DLT), Recommended Phase 2 Dose (RP2D), Maximum Concentration (Cmax), Intravenous (IV), once every 2 weeks (Q2W), Non Small Cell Lung Cancer (NSCLC)

Baseline Characteristics

Patient Characteristics	N (%)
Total Number of patients	16 (100)
Female/ Male	6 (37) / 10 (62.5)
Age, median (range in years)	63 (50-78)
Race/Ethnicity	
African American	1 (6.25)
White	14 (87.5)
Hispanic or Latino	1 (6.25)
Other	1 (6.25)
Cancer Types	
Colorectal	5 (31.25)
Head and Neck	3 (18.75)
Pancreatic	2 (12.5)
NSCLC	1 (6.25)
Breast	1 (6.25)
Bladder	1 (6.25)
Gastric	1 (6.25)
Mesothelioma	1 (6.25)
Endometrial	1 (6.25)

Table 2: CI-8993-101 Patient Baseline Characteristics

Cytokine Profile

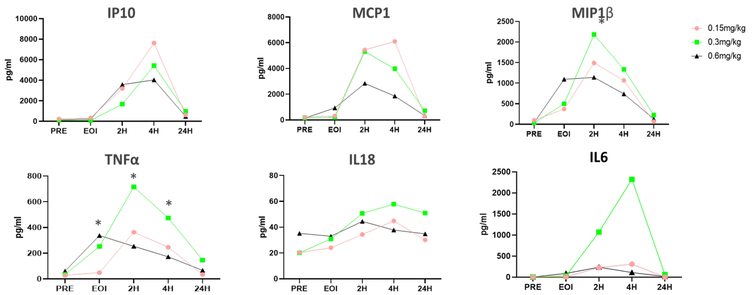
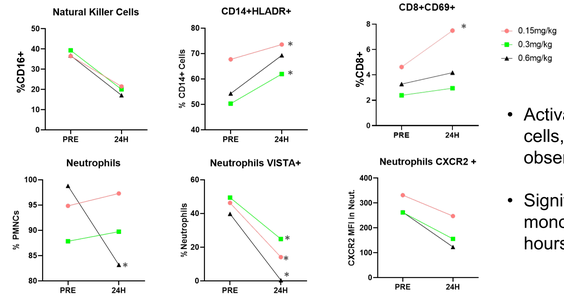


Figure 2: Average cytokine concentration at CI-8993 pre and post infusion at 0.15 mg/kg (n=7), 0.3 mg/kg (n=5) and 0.6 mg/kg (n=4) dose. (* P≤0.05)

- Results indicate a rapid, but transient, increase of inflammatory mediators including plasma cytokines (IL6, IL18) and chemokines (IP10, MCP1) (* P≤0.05)
- Soluble markers such as TNFα and MIP1β present differences between cohorts at 4 hours after treatment (* P≤0.05)
- Patients from CI-8993 cohort 3 (0.6 mg/kg) exhibit lower cytokine levels when compared to cohort 1 and 2 (0.15 and 0.3 mg/Kg)

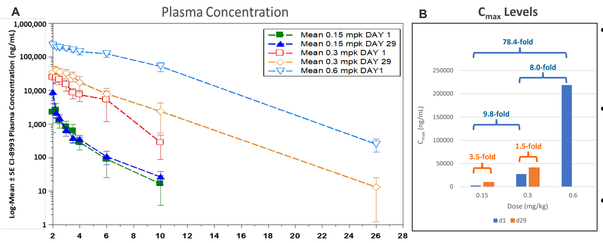
Whole Blood Immunophenotyping



- Activated T cells, suppression of CD16 on NK cells, and increased HLA-DR on monocytes, are observed between the three cohorts
- Significant changes in neutrophils and activated monocytes populations are observed after 24 hours of initial treatment (* P≤0.05)

Figure 3: Average values of immunophenotypes at baseline and 24 hours after CI-8993 infusion at 0.15 (n=7), 0.3 (n=5) and 0.6 (n=4) mg/kg dose

CI-8993 Plasma Concentration



- Greater-than-proportional exposure increases with higher and multiple doses of CI-8993
- Increased half-life at higher doses suggests the ability to saturate the "VISTA sink" consistent with preclinical PK-distribution study predictions (5)
- No anti-drug antibodies were detected in any of the cohorts

Figure 4: A. Arithmetic mean of the concentration-time profiles of CI-8993 following iv administration at 0.15, 0.3, and 0.6 mg/kg to patients with solid tumors in cycle 1. B. Cmax levels versus CI-8993 dose. (* P≤0.05)

Conclusions

- In CI-8993-101 study, patients were safely managed without DLTs at 0.15, 0.3 and 0.6mg/kg dose levels
- Evidence of a rapid, transient and systemic inflammatory response is indicated by an increase of the inflammatory soluble mediators
- Increase on activated immune cells, and decrease on suppressor cells suggest an early immune response with different anti-tumoral mechanisms
- Lower cytokine levels in patients from cohort 3 (0.6 mg/kg) may be associated with the higher step dosing regimen used in this cohort
- Saturation kinetics suggest favorable drug bioavailability at higher dose levels
- CI-8993-101 study is open and currently enrolling patients at 1mg/kg dose. Further evaluation of the peripheral immune system and PK properties, will be performed as we move toward the determination of RP2D

References
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Acknowledgment
We would like to thank the patients, their families and caregivers for their invaluable contribution and participation in this study
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