761 PHARMACOKINETIC AND PHARMACODYNAMIC DATA FROM A PHASE 1 STUDY OF CI-8993 ANTI-VISTA ANTIBODY IN PATIENTS WITH ADVANCED SOLID TUMORS

[1]Randolph Noelle*, [2]Melissa Johnson, [3]Jordi Rodon, [4]Marjorie Zauderer, [1]Lionel Lewis, [5]Mariano Severgnini, [5]Jefferson Parker, [5]Maureen Lane, [5]Reinhard von Roemeling, [6]Alex Martin, [7]Michael Molloy, [5]Robert Martell, [8]Tong Dai. *[1]Geisel School of Medicine at Dartmouth, Hanover, NH, USA; [2]Tennessee Oncology, Nashville, TN, USA; [3]MD Anderson Cancer Center, Houston, TX, USA; [4]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [5]Curis Inc, Lexington, MA, USA; [6]Curis Inc/Tufts Medical Center, Lexington, MA, USA; [7]ImmuNext Inc, Lebanon, NH, USA; [8]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA*

Background V-domain Ig suppressor of T-cell activation (VISTA) is a novel negative checkpoint ligand that suppresses T cell activation forcing cells into a quiescent state. In pre-clinical studies anti-VISTA monotherapy has been shown to promote anti-tumor immunity. The impact of anti-VISTA therapy within the tumor microenvironment (TME) resulted in upregulated antigen-presentation pathways, reduced myeloid mediated immune suppression, enhanced lymphocyte infiltration and, with the promotion of co-stimulatory genes, reduced regulators of T cell quiescence and reduced tumor growth. In this work, we present pharmacokinetic (PK) data, and describe pharmacodynamic (PD) changes in the immune system in patient samples from the Phase 1 CI-8993-101 study, open label, dose escalation study (NCT04475523) administering an IgG1 anti-VISTA antibody (CI-8993) to patients with solid tumors.

Methods Patients were enrolled into cohorts that are structured to receive step-dosing regimens before administering a single 'full dose" of CI-8993. Cytokine release related toxicities were successfully managed with initial step-dosing and corticosteroids. The CI-8993 full doses ranged from 0.15 mg/kg to 0.6mg/kg in three separate cohorts. Immune-related PD, and PK analyses were performed on blood/serum from 17 patients at time points following step-dose, and full dose administration of CI-8993.

Results Data indicates a rapid, but transient, increase in cytokines and chemokines (e.g., IL6, IL18, IP10, MCP1) ($P \leq 0.05$). Soluble markers (TNFα and MIP1β) present differences between cohorts 4 hours after treatment ($P \leq 0.05$) without a clear dose-response relationship. We observed changes in neutrophils and activated monocytes populations after 24 hours of initial treatment ($P \leq 0.05$). Activated T cells (CD8+CD69+), decreased CD16 on NK cells, and increased HLDR expression on monocytes were observed between cohorts ($P \leq 0.05$). A greater than dose-proportional exposure increased with higher doses of CI-8993.

Conclusions CI-8993 was well tolerated and no DLTs were observed in the cohorts studied. An increase in pro-inflammatory cytokines, and anti-cancer immune cell phenotypes was observed. The lack of a dose-response effect in cytokine concentrations between cohorts is likely related to the higher step-dose regimen in cohort 3 (0.6mg/kg) that is dampening the cytokine release following the first full dose. The increase in pro-inflammatory phenotypes and soluble mediators post-treatment suggests an early immune response with different anti-tumoral mechanisms. Saturation PK indicates a favorable drug bioavailability at higher doses with an increased half-life. This suggests the ability to saturate the VISTA sink consistent with pre-clinical studies.[1] Further evaluation of the immune system and PK properties of CI-8993 will be performed as we continue enrollment to determine the RP2D.

Trial Registration NCT04475523

REFERENCE

1. Wichmann CW, Burvenich IJG, McDonald AF, Scott FE, Guo N, Rigopoulos A, Soikes R, Angelides S, von Roemeling R, Scott AM. Preclinical evaluation of anti-VISTA antibody CI-8993 in a syngeneic huVISTA-KI model. SITC Abstract 2021: #324

Ethics Approval Yes, this study has obtained ethical approval and participants have given full consent

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