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 CTLA4 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 proliferation in the periphery, enhanced the infiltration 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 tumor mutational burden, fragment crystallizable receptors (FcRs), alleles, and post-translational modifications, up-regulating MHC class II, and PD1 ligand (PD-L1) by immunohistochemistry (IHC) staining.

Methods and Study Design (NCT04475523)

1) 18 + 3 weeks of age
2) HIV, hepatitis B, and/ or C, active severe intercurrent medical illness
3) Relapsed/refractory solid tumor (non-hematologic) ≤ 15 mg/day of prednisone equivalent or immunotherapy for > 6 weeks
4) Metastatic or uncontrolled CNS disease
5) History of personal or family history of HLH or MAS
6) Adequate organ and bone marrow function
7) Immune-related AE ≥ grade 3

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.

3 + 3 Design

The dose escalation process has a 3+3 design. Patients with solid tumor malignancy (non-hematologic) that is metastatic or unreactable 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.

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 immunologic compounds, which has been designated as an adverse event (AE) of special interest and grouped together with infusional related reactions (IRRs) as treatment-emergent AE and will be closely monitored in this study. In addition to administration of a desensitizing stage 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

1) Preclinically, CI-8993 shows anti-tumor efficacy and synergy with other checkpoint inhibitors (CPIs) through TME modulation via increased peripheral tumor-specific T cells, monocytes, and T cell activation.

2) This may prevent or overcome adaptive VISTA-related resistance to CPIs.

3) CI-8993 is the first monoclonal antibody targeting VISTA to be tested in human solid tumor patients. NCT04475523 is currently recruiting patients.

Further Information

ClinicalTrials.gov identifier: NCT04475523
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References

5) NCT04475523

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