Phase 1 trial of CA-170, a novel oral small molecule dual inhibitor of immune checkpoints PD-1 and VISTA, in patients with advanced solid tumors or lymphomas

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Introduction

- To determine the pharmacodynamic effects of CA-170 on selected immune checkpoints that negatively regulate T-cell function and regulate the anti-tumor immune response (Lu et al. 2015, PNAS 112:6802-7).
- VISTA is highly expressed on tumor infiltrating myeloid cells (i.e. macrophages, MDSCs) and may be expressed on tumor infiltrating T cells.
- VISTA and PD-L1 expression increases on tumor infiltrating immune cells following ipilimumab treatment, suggesting upregulation of alternative checkpoints (Gao J et al, 2016).

CA-170: First-in-class, small molecule oral PD-1/L1 & VISTA antagonist

In Vitro Rescue of Suppressed Human T Cell Effector Function

In Vivo Anti-tumor Efficacy

Oral Bioavailability

Study Rationale

- Preclinical and clinical data show that the different immune checkpoints function via distinct, non-redundant pathways suggesting that a combination therapy targeting multiple checkpoints may improve anti-tumor activity.
- Upregulation of alternative immune checkpoints may result in the adaptive resistance to the tumor immune checkpoint monotherapy. Targeting more than one immune checkpoint may overcome this adaptive resistance.
- A combination therapy targeting the PD-1/L1 and VISTA pathways is a promising treatment strategy that offers a better potential for patients to achieve objective response over monotherapy alone.

Study Objectives

**Primary**

- Phase 1a: Dose Escalation
  - To determine the safety and tolerability, dose-limiting toxicities (DLTs), maximum tolerated dose (MTD), and recommend Phase 2 dose (RP2D) of daily oral CA-170 in patients with advanced solid tumors or lymphomas

- Phase 1b: Dose Expansion
  - To confirm the safety and tolerability of oral CA-170 in patients with advanced solid tumors or lymphomas shown to be sensitive to anti-PD-1 or anti-PD-L1 therapy and/or in tumor types known to express PD-L1 or VISTA, such as: melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), Hodgkin lymphoma (HL), urothelial carcinoma (UC), and head and neck squamous cell carcinoma (SCCCHN).

**Secondary**

- To assess the pharmacokinetic (PK) profile
- To assess the preliminary anti-cancer activity
- To explore the pharmacodynamic effects of CA-170 on selected markers of immune modulation in peripheral blood and tumor tissue
- To assess the potential association between target-related biomarkers and clinical efficacy

Study Design

**Phase 1b: Dose Expansion**

- ~250 patients with advanced cancers or lymphomas shown to be sensitive to anti-PD-1 or anti-PD-L1 therapy and/or in tumor types known to express PD-L1 or VISTA, such as: melanoma, NSCLC, RCC, HL, UC, and SCCCHN.

**Study Status**

- This study was initiated in June 2016
- As of May 2017, the study has treated a total of 20 patients across 6 dose levels with 800 mg QD as the highest dose level evaluated so far. There have been no reports of DLTs - the study continues with further dose escalation and expansion
- More information is available at www.clinicaltrials.gov (NCT02812875)

**References**
