Pharmacodynamic effects of CA-170, a first-in-class small molecule oral immune checkpoint inhibitor (ICI) dually targeting V-domain Ig suppressor of T-cell activation (VISTA) and PDL1

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Introduction
CA-170 is a first-in-class small molecule oral inhibitor of the V-domain Ig suppressor of T-cell activation (VISTA) and PD-L1/2 immune checkpoint pathways currently in phase 1 (NCT02812875) 1 and phase 2 clinical trials. VISTA is distinct from PD-1/L1 checkpoint pathway and can independently suppress T cell responses 3. It is expressed on both immune and tumor cells 4,5,6,7,8 and is found to be upregulated in cancers as a potential resistance mechanism after therapy with immune checkpoint inhibitors (ICIs). 9 As such, it has been considered a target for cancer immunotherapy. Pre-clinical studies have demonstrated CA-170 can modulate immune cell activity both in vitro and in vivo. Therefore demonstration of clinical pharmacodynamic (PD) activity of CA-170 is an important goal of the phase 1 clinical trial. Preliminary data from the PD analysis are reported here.

Methods
- Data from peripheral blood samples taken at baseline and 24 hours post C1D1 dose were presented for immune phenotyping of circulating T-cell populations. Activation markers of CD69, CD134 and granzyme were also validated on 10 healthy volunteers to determine if procedures induced spontaneous activation and to set the threshold for the fold change required to determine if change is outside of a normal change.
- Archived tumor tissue was acquired on all patients.
- Paired tumor biopsies (baseline and Cycle 2) were collected when accessible and feasible. Both immunohistochemistry (IHC) staining for CD8, CD11b and VISTA and a Nanostring Immune profiling panel were run on paired tumor samples. IHC was semi-quantitated using the Aquascoring system (Yale).
- Changes in CD8 and VISTA expression in tumor tissue following CA-170 treatment.
- Changes in IFN-γ and induced genes in tumor.
- Conclusion and Future Directions

Changes in IFN-γ and Induced Genes in Tumor

The expression IFN-γ and IFN-γ induced genes are shown. The Log2 normalized data from post-dose tumor tissue was examined and a difference of 2 fold considered a change (red box). Of the 10 patients, biopsies available for this analysis, 7 had at least one IFN-γ related gene upregulated.

Conclusion and Future Directions

- CA-170 induced peripheral T cell activation.
- Increased number of CD8+, VISTA+ and CD11b+ T cells was observed in tumor tissue following CA-170 treatment.
- CA-170 treatment increased the tumor expression of IFN-γ and induced transcripts.
- Nanostar analysis also showed CA-170 may be affecting Th subsets and myeloid populations.
- Clinical development of CA-170 is on-going with evaluation of potentially pharmacologically active BID dose in VISTA expressing tumors, including epithelioid mesothelioma which has strikingly higher VISTA expression than other solid tumors. Further PD analysis will be done in VISTA rich mesothelioma patients to determine if change is outside of a normal change.

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