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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/L2 immune checkpoint pathways currently in phase 1 (NCT02812875)[1] and phase 2[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 (ICI)[9,10]. 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.

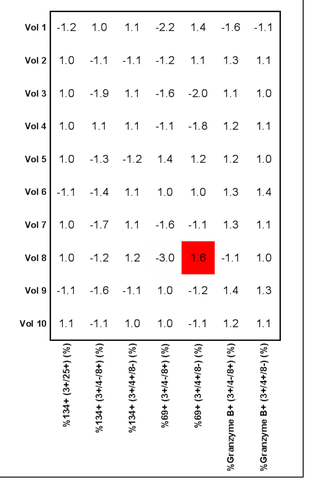
Methods

- 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).

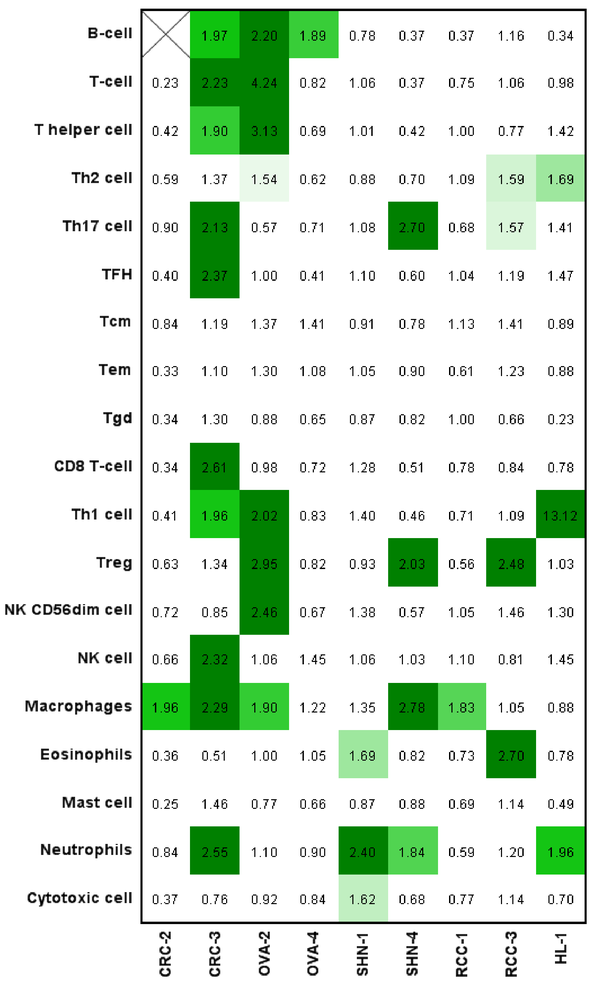
Evidence of CA-170 Immune Modulation Activity In Human Peripheral Blood

	%134+ (3+/25+) (%)	%134+ (3+/4-/8+) (%)	%134+ (3+/4+/8-) (%)	%69+ (3+/4-/8+) (%)	%69+ (3+/4+/8-) (%)	%Granzyme B+ (3+/4+/8+) (%)	%Granzyme B+ (3+/4+/8-) (%)
CRC-2	1.25	3.89	2.16	-1.51	2.87	1.06	-1.70
CRC-3	1.51	11.12	2.44	2.77	2.82	1.15	1.16
CRC-4	-12.57	1.01	1.10	-1.31	-2.02	1.61	1.57
CRC-5	1.08	-1.80	-1.01	1.85	2.01	1.04	1.14
CRC -6	1.97	-1.80	-1.21	-1.29	1.13	-1.75	-4.63
CRC-7	-11.61	-3.53	-4.05	-4.24	-3.83	1.27	3.07
CRC-9	2.23	1.03	1.30	-1.06	-1.06	1.35	1.62
ANL-1	1.98	2.86	2.83	147.86	6.40	-2.31	-2.82
EOS-2	1.16	-1.78	-1.09	1.68	-1.36	1.24	-2.32
MEL-1	-1.02	3.12	1.47	3.20	1.52	-1.02	-1.18
MEL-2	-1.55	-1.22	-1.43	-1.20	2.44	1.09	1.40
MEL-3	-1.31	-1.39	1.01	1.20	1.80	-1.02	1.29
MRK-1	1.20	1.39	1.65	3.65	2.83	1.11	1.21
NSL-1	-1.06	1.03	1.07	1.04	1.34	-1.26	1.46
NSL-4	-1.14	-1.96	-1.22	-1.37	-2.07	1.06	1.51
NSL-6	1.18	1.08	-1.03	-1.15	1.80	-1.02	-1.07
NSL-7	1.16	-1.97	1.06	-2.13	-3.49	-1.02	-1.20
NSL-8	-1.39	-1.53	1.02	-2.45	-1.19	1.09	-1.27
NSL-9	-1.09	1.24	1.26	-1.75	-1.56	-1.07	-1.04
NSL-11	1.37	2.83	2.56	-2.42	2.09	14.40	6.57
SHN-1	1.03	1.81	1.35	-1.27	-1.34	-1.01	-1.12
SHN-2	-1.92	1.92	-1.03	1.01	-2.49	-1.05	-1.29
SHN-4	1.86	-1.14	-1.13	-1.78	-1.74	-1.01	1.23
SHN-5	-1.39	-3.56	-5.57	-1.14	-1.96	-179.28	-9.43
SHN-6	-2.90	-1.07	1.01	-3.58	-6.25	-1.27	-2.10
OVA-1	1.11	1.76	1.57	-1.47	1.11	-1.06	-2.16
OVA-2	1.03	1.31	1.14	-1.52	-1.65	1.01	1.28
OVA-3	-1.15	-1.55	-1.40	-1.89	-1.06	-1.00	1.03
OVA-4	-1.79	-54.23	-3.08	3.73	-1.38	-101.08	-55.57
BRT-1	1.44	1.83	1.88	2.62	3.31	1.07	1.85
LDC_1	2.27	3.52	3.18	3.37	1.33	2.55	1.06
NEP-1		-7.15	-4.12	-2.13	-2.64	1.71	2.44
HCC_1	-2.02	-43.71	-3.75	1.31	1.22	-298.36	-37.16
RCC-1	-1.38	1.59	1.05	-1.29	-1.50	-1.03	-1.21
RCC_2	1.27	1.00	1.16	1.91	5.37	1.02	-1.02
FL-1	-1.73	-22.39	-2.10	-1.00	-1.50	-5.02	3.43
HL-1	-1.15	-1.15	1.05	-3.13	-2.31	1.11	1.79
HL-2	24.42	1.77	127.94	8.64	65.88	-1.74	-1.50

Fold changes of peripheral activation markers as determined by flow cytometry 24 hours after the first dose are presented. A ≥1.5 fold (green square) increase in the percentage of cells expressing the activation markers was determined to be different as based on validation data of 10 healthy individuals. Of the 38 patients with available data, 29 had at least one T cell activation marker increased ≥1.5 fold with 14 having more than one activation marker increased on peripheral T cells

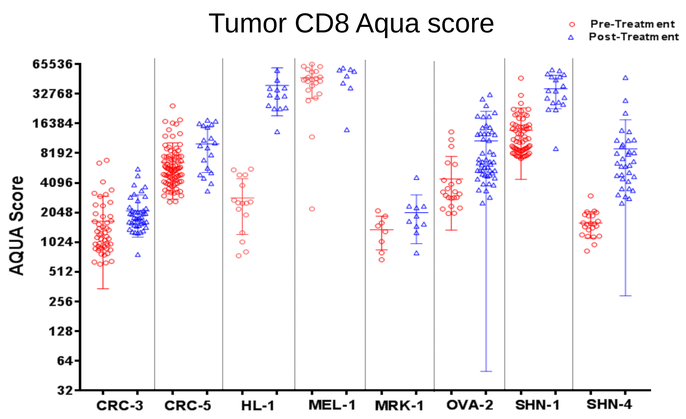


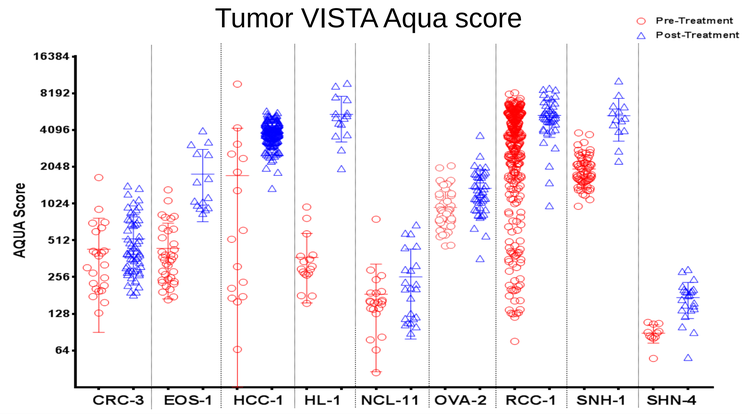
Alterations in Tumor Populations by Nanostring

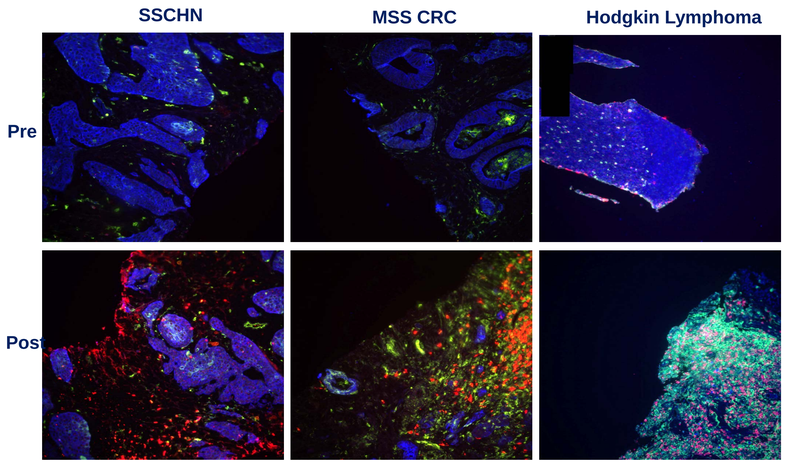


Changes in Cycle2 in tumor mRNA transcripts post CA-170 treatment. Populations were determined using the Nanostring defined panels. A ≥2 fold increase (green square) in the normalized Log2 data was considered a change.
All patients were naïve to prior therapy with an immune checkpoint inhibitor except CRC-2 and OVA4

Changes in CD8 and VISTA Expression in Tumor Tissue Following CA-170 Treatment



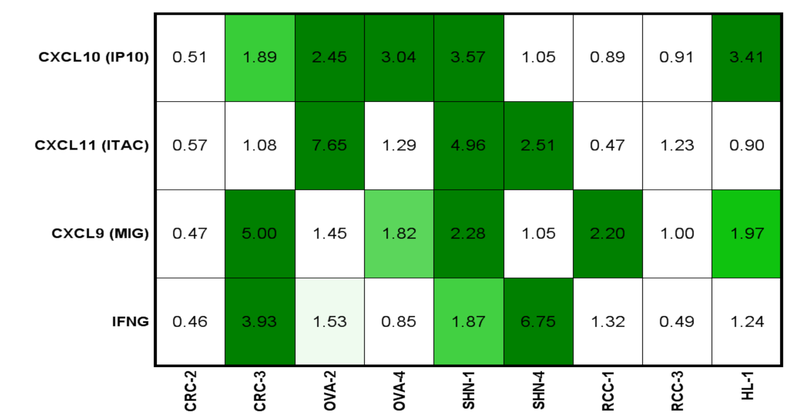




Red=CD8; Green=VISTA; Yellow=CD8+VISTA; Blue=cytokeratin

- Aqua score analysis of IHC from pre and post dose tumor samples. Each circle represents the automated quantification (AQUA) score of a single view field of the tumor biopsy for each patient.
- Patients with samples with less than 5 fields of view in the IHC in either pre or post-treatment biopsy were not included.
- In both panels only patients with a mean increase in either CD8 or CD11b post CA-170 treatment were displayed. Of the initial 19 available paired biopsies for CD8 staining, 8 showed a mean increase in CD8. Of the 15 available paired biopsies for VISTA staining, 9 showed an increase in VISTA staining.

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 pre-post dose tumor tissue was examined and a difference of 2 fold considered a change (red box). Of the 9 paired 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.
- Nanostring 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[4]. Further PD analysis will be done in VISTA rich mesothelioma patients to confirm the observations seen in non-selective tumor types, and also to establish the relationship of PD effect to anti-tumor activity in the more selective patient populations.

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