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CA-170, A First in Class Oral Small Molecule Dual Inhibitor of Immune Checkpoints PD-L1 and VISTA, Demonstrates Tumor Growth Inhibition in Pre-Clinical Models and Promotes T Cell Activation in Phase 1 Study

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Introduction

- The programed death ligand 1 (PD-L1) and V-domain Ig suppressor of T-cell activation (VISTA) are functionally independent immune checkpoints that negatively regulate T-cell function and the anti-tumor immune response (Liu J et al. 2015. *PNAS*. 112(21):6682-7).
- 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. 2017. *Nat Med*. doi:10.1038/nm.4308).
- Non-clinical studies in animal models of cancer show that blocking both the PD-1/L1 and VISTA pathways results in enhanced anti-tumor activity over that of blocking either pathway individually (Liu J et al. 2015. *PNAS*. 112(21):6682-7).
- CA-170 is a first-in-class, synthetic, orally bioavailable, small molecule that dually targets PD-L1 and VISTA pathways and showed anti-tumor activity in preclinical models.
- Information presented here is emerging clinical data from the first-in-human study (update since April 2017).

Study Design

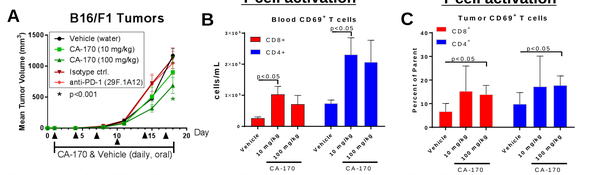
- Eligible patients were aged ≥18 years with advanced solid tumors or lymphomas, adequate organ function, and ECOG PS 0–1.
- Patients receive once daily (QD) oral CA-170 continuously in 21-day cycles.
- Enrollment initially followed accelerated titration and then switched to a 3+3 design.
- Treatment continues until unacceptable toxicity or disease progression.
- Tumor response was evaluated every other cycle in the first 6 treatment cycles and then every 3 cycles beyond cycle 6 per Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST) and Immune-related Response Criteria (irRC) for solid tumors or Revised Cheson Response Criteria for Malignant Lymphoma.
- Selected dose levels were expanded to better understand their pharmacokinetics (PK), pharmacodynamics (PD), immune effects, and anti-tumor activity.

Objectives

- Primary: safety, maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D).
- Secondary: PK and anti-tumor activity.
- Exploratory: biomarkers and PD effects in peripheral blood and tumor tissues.

Non-Clinical Results

CA-170 Efficacy



Increased peripheral T cell activation

Increased tumor T cell activation

Figure 1: CA-170 efficacy and T cell activation in the B16/F1 syngeneic mouse tumor model

A) Mice implanted with subcutaneous B16/F1 melanoma tumor cells were treated as indicated. The triangles indicate the days of antibody dosing. Tumor growth inhibition at Day 18 is 23%, 41% and 7% for CA-170 (10 mg/kg), CA-170 (100 mg/kg) and anti-PD-1 (100 µg/day), respectively. **B)** In a separate experiment, the number of CD69⁺ peripheral blood T cells were analyzed following 5 days of oral CA-170 dosing in B16/F1 tumor bearing mice. **C)** Tumor CD8⁺CD69⁺ or CD4⁺CD69⁺ T cells from B16/F1 tumors following 6 days of oral dosing. P-values were determined by Student's t-tests. Panels **A** and **C**: Ager et al., 2016 *J. Immunother. Cancer* 4, 107–221.

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Clinical Results

- Baseline and disease characteristics for 34 enrolled patients are presented in **Table 1**.
- In this presentation, patients are grouped into 3 groups:
  - Group 1: Immune checkpoint inhibitor (ICI) therapy naïve patients with tumor types for which there is at least one FDA approved ICI (anti-PD-1, PD-L1, CTLA4 antibodies). Prior treatments in this group were non-ICI therapies. Tumor types in this group include melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (clear cell type, ccRCC), urothelial cancer, head and neck squamous cell carcinoma (SCCHN), Hodgkin Lymphoma (HL), and any tumor that is Microsatellite Instability-High or Mismatch Repair Deficient as documented by a prior test. Patients with these tumor types can be enrolled no matter how many prior lines of therapies a patient received. The majority of patients in this group were enrolled from study sites outside the US.
  - Group 2: ICI naïve patients with a tumor type for which there is no ICI approved by the FDA or any other health authority.
  - Group 3: Patients with prior exposure to at least one line of ICI therapy.

Table 1: Baseline Patient and Disease Characteristics

Characteristics	Group1 N = 17	Group2 N = 13	Group3 N = 4	Overall N = 34
Tumor type with at least one FDA approved ICI	Yes	No	Both	Both
Prior ICI therapy	No	No	Yes	Both
Gender, n (%)				
Male	13 (76)	6 (46)	1 (25)	20 (59)
Female	4 (24)	7 (54)	3 (75)	14 (41)
Age, median (range)	58 (27-80)	63 (26-86)	61 (58-62)	61 (26-86)
ECOG PS, n (%)				
0	6 (35)	4 (31)	1 (25)	11 (32)
1	11 (65)	9 (69)	3 (75)	23 (68)
Prior lines, median (range)	2 (0-8)	7 (0-9)	4.5 (2-7)	7 (0-9)
Tumor type, n (%)				
NSCLC	7 (41)	0	0	7 (20)
Ovarian	0	4 (31)	1 (25)	5 (15)
Hodgkin lymphoma	2 (12)	0	0	2 (6)
Non-Hodgkin Lymphoma	0	2 (15)	0	2 (6)
SCCHN	3 (18)	0	0	3 (9)
ccRCC	3 (18)	0	0	3 (9)
Colorectal (MSS)	0	1 (8)	1 (25)	2 (6)
Melanoma	2 (12)	0	0	2 (6)
Esophageal	0	1 (8)	1 (25)	2 (6)
Breast	0	2 (15)	0	2 (6)
Other*	0	3 (23)	1 (25)	4 (12)

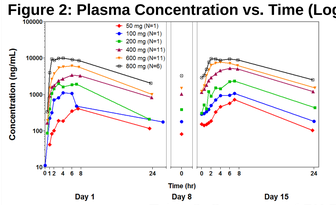
* One each of lacrimal duct carcinoma, hepatocarcinoma, Merkel cell carcinoma (MCC, all Group 2), and anal cell carcinoma (Group 3)

Clinical Safety Findings

- 28 patients evaluable for safety endpoints.
- No DLTs or irAEs have been reported thus far for the dose range 50 – 800mg; MTD and RP2D have not been established.
- The treatment-emergent AEs (TEAEs) predominantly Grade 1 or 2 and self-limiting:
  - The most frequently (>10%) reported TEAEs were nausea (24%), fatigue (21%), constipation (18%), anemia (15%), chills (15%), vomiting (15%), fever (15%), gastritis (15%), headache (12%), insomnia (12%), and tumor pain (12%).
- Treatment-related AEs were primarily Grade 1 and 2 events.
  - The most frequently (>10%) reported related AEs were fatigue (15%)
  - No drug related AEs resulted in study discontinuation or dose interruptions.
- A total of 12 SAEs have been reported (all unrelated to CA-170).
- Two death events were reported during study follow-up after the patients discontinued the study treatment. In both cases, the death events were assessed by the investigators to be caused by disease progression and not related to CA-170.

Pharmacokinetics

Figure 2: Plasma Concentration vs. Time (Log Scale)



- Systemic exposures (Cmax & AUC) generally increased proportionally with increasing doses from 50 to 800 mg.
- Inter-patient variability is within the expected range, given the potential impacting variables of oral administration, QD dosing and a highly heterogeneous patient population enrolled thus far.

Table 2: Summary of PK Parameters on Day 1

PK Parameters		50 mg (N=1)	100 mg (N=1)	200 mg (N=1)	400 mg (N=11) Mean ± SD	600 mg (N=11) Mean ± SD	800 mg (N=6) Mean ± SD
Tmax	hr	7.3	4.0	3.0	6.2±2.0	4.9±1.8	3.8±2
Cmax	ng/ml	412	1107	1998	3744±991	7018±3355	11865±7775
AUCall	hr*ng/ml	5681	11475	27488	51166±14292	87548±42685	149221±111023
T1/2	hr	8.7	9.5	5.3	8.5±2.9	7.6±3.2	8.3±2.5

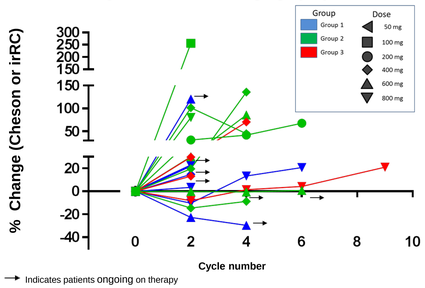
Anti-Tumor Activity

- 21 patients are evaluable for antitumor activity with at least one post-treatment restaging (**Table 3, Figure 3**):
  - 13 patients showed stable disease (SD) per RECIST/irRC with 8 still ongoing on treatment, including 4 patients on treatment > 6 cycles. 4 of the SD patients demonstrated reductions in target lesion size (Group 1: 1 melanoma and 1 NSCLC at 600 mg; Group 2: 1 ovarian at 400 mg; and Group 3: 1 esophageal cancer at 800 mg).
  - 8 patients showed PD as their best response.
- 5 patients are still pending 1st restaging.

Table 3: Summary of Anti-Tumor Activity Per irRC

Group	Treated (N = 34)	Ongoing (N=13)	Median Cycles of Treatment (range)	Evaluable for Anti-tumor Activity (N = 21)	# of SD (N=13)	# of Response	Patients with Target Lesion Shrinkage (N=4)
Group 1	17	10	2.3 (0.7-7.4)	8	6	0	2
Group 2	13	2	2.0 (0.4-9.10)	9	5	0	1
Group 3	4	1	3.0 (2.0-9.29+)	4	2	0	1

Figure 3: Tumor Restaging by Cycle



Pharmacodynamics (Peripheral Blood)

CD134 (OX40) Activation marker in peripheral blood

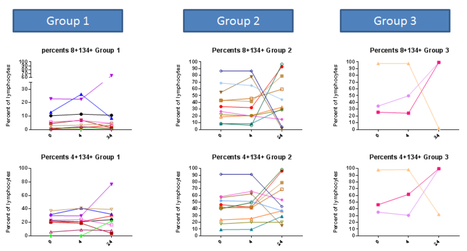
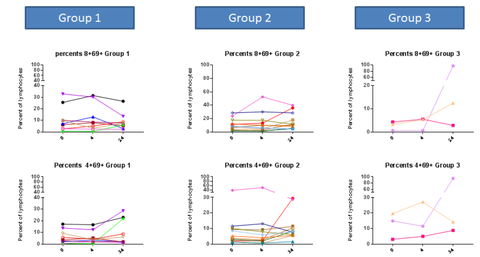


Figure 4: Evidence of peripheral T cell activation was observed with an increased proportion of circulating CD8⁺ and CD4⁺ T cells expressing activation markers, CD69 and CD134.

Pharmacodynamics (Peripheral Blood)

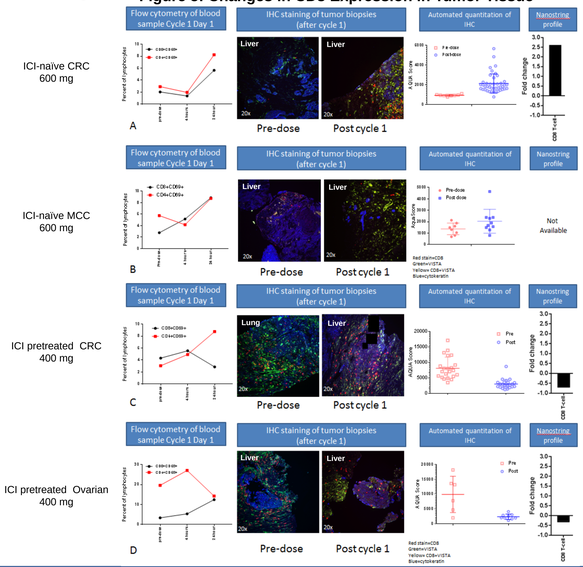
CD69 Activation marker in peripheral blood



Pharmacodynamics (Tumor Biopsy)

- To date, pairs of pre-/post-treatment tumor biopsies have been examined for changes in CD8 expression (**Figure 5**):
  - 2 pairs (A & B) from patients in Group 2 have demonstrated an increase in the presence of CD8+ cells in the tumor
  - 2 pairs (C & D) were from patients in Group 3 and demonstrated no changes in CD8 staining.

Figure 5: Changes in CD8 Expression in Tumor Tissue



Conclusions and Future Directions

- Pre-clinically, CA-170 significantly inhibits tumor growth in the B16/F1 syngeneic mouse tumor models. Increased number of intra-tumor activated CD8⁺ T-cells positively correlate with tumor growth inhibition in these models.
- Clinically, the MTD and RP2D have not yet been established.
  - The emerging clinical data suggest that CA-170 has an acceptable safety profile with approximately dose proportional PK profile and preliminary evidence of peripheral immune modulation at the dose levels evaluated
  - Data from a small number of patients shows preliminary signs of anti-tumor activity, including tumor shrinkages and prolonged stable disease.
- These preclinical and clinical data warrant the continued clinical development of CA-170. Dose escalation is ongoing. Expansion cohorts in selected indications are planned.

Acknowledgements

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