CA-170, an Oral Small Molecule Immune Checkpoint Antagonist, Promotes T Cell Immune Activation and Inhibits Tumor Growth in Pre-clinical Models of Cancer

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Introduction

CA-170 is a small molecule, orally bioavailable antagonist of the VISTA/PD-1H and PD-L1 immune checkpoint pathways which is currently undergoing Phase I clinical testing. CA-170 was selected as clinical candidate based on its ability to antagonize T cell immune suppression (human or mouse) mediated by VISTA/PD-1H, PD-L1 or PD-L2 (see tables below).

Mouse Splenocytes

	Proliferation Rescue (*in vitro*) EC_{50} (nM)		IFN-γ Rescue (*in vitro*) EC_{50} (nM)	
Test Compound	PD-L1	PD-L2	PD-L1	PD-L2
CA-170	16.32	16.56	33.79	54.98
Anti-PD-1 antibody (clone J43)	17.05	10.45	12.59	37.58

Human PBMCs

	Proliferation Rescue (*in vitro*) EC_{50} (nM)		IFN-γ Rescue (*in vitro*) EC_{50} (nM)		
Test Compound	PD-L1	PD-L2	PD-L1	PD-L2	VISTA/PD-1H
CA-170	43.47	40.57	56.43	149.0	49.35
Anti-PD-1 antibody (clone J116)	18.87	22.78	27.24	66.87	N/T
Anti-VISTA antibody (clone 730802)	N/T	N/T	N/T	N/T	25.82
VISTA isotype ctrl.	N/T	N/T	N/T	N/T	628.3

N/T = Not Tested

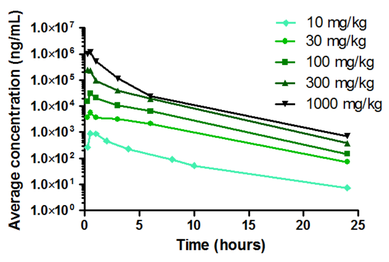
CA-170 non-clinical safety summary:

- ❖ No mortality, test item-related changes, or microscopic pathology changes in tissues observed
- ❖ the maximum tolerated dose (MTD) was NOT reached
- ❖ NOAEL (no observed adverse effect level) was >1000 mg/kg/day.

Here we present the relationship between CA-170 non-clinical and preliminary clinical data. This presentation contains interim data (Nov/01/2016) from the ongoing CA-170-101 Phase 1 clinical trial which was obtained after the abstract submission.

Oral CA-170 pharmacokinetic profile in mice

A



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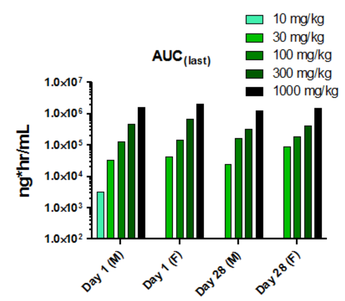

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	Balb/c mice				
Dose (mg/kg)	10	30	100	300	1000
$T_{1/2}$ (hours)	4.57	3.94	3.29	3.02	2.70
T_{max} (hours)	0.5	0.5	0.5	0.5	0.5
C_{max} (ng/mL)	890	5572	31821	261823	1793147
AUC_{last} (hr*ng/mL)	**3170**	**38668**	**136696**	**575297**	**1896148**

A) CA-170 plasma concentrations were measured at various time points in Balb/c mice following a single oral dose. The data shown are the average plasma concentrations of male and female mice (n=6), except 10 mg/kg which is from males only (n=3). **B)** CA-170 plasma exposure was calculated from male (M) and female (F) mice orally dosed for 1 or 28 consecutive days. **C)** CA-170 pharmacokinetic parameters in Balb/c mice (averaged male & female) following the administration of the first dose. CA-170 exposure is greater than dose proportional between 10 mg/kg and 300 mg/kg in Balb/c mice.

CA-170-101 Phase 1 Clinical Trial Summary

Study conducted in:	United States, Europe & Asia
Clinical Trials.gov identifier:	NCT02812875
Trial Status:	Currently recruiting patients
Conditions:	Advanced solid tumors & lymphomas
Starting dose:	50 mg QD, calculated based on the minimum anticipated biological effect level (MABEL).

Oral CA-170 pharmacokinetic profile in humans (NCT02812875)

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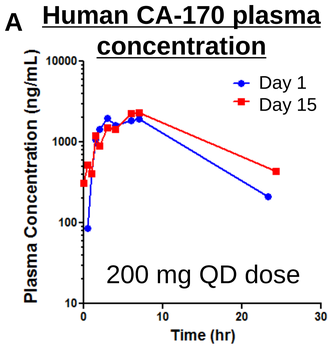

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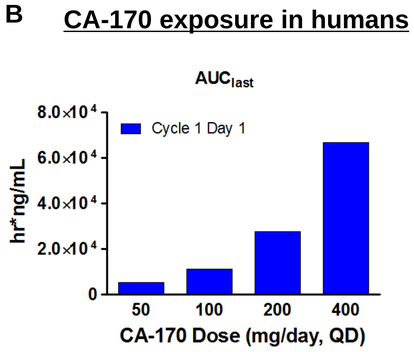

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	Human Cycle 1 Day 1				Cycle 1 Day 15
Dose (mg)	50	100	200	400	200
$T_{1/2}$ (hours)	8.7	9.6	5.3	12.9	7.1
T_{max} (hours)	7.4	4	3	4	7
C_{max} (ng/mL)	412	1107	1998	4100	2337
AUC_{last} (hr*ng/mL)	**5197**	**11019**	**27488**	**66664**	**33998**

Preliminary pharmacokinetic data from the CA-170 Phase 1 trial. **A)** CA-170 plasma concentrations after 1 dose (Day 1) and after 15 consecutive doses (Day 15). **B)** CA-170 plasma exposure was calculated from a sample series collected on Day 1 following the first oral dose at 50 mg (n=1), 100 mg (n=1), 200 mg (n=1) or 400 mg (n=1). **C)** CA-170 pharmacokinetic parameters in humans.

Non-clinical CA-170 efficacy and T cell activation in syngeneic mouse tumor models

Anti-tumor efficacy in the B16/F1 model

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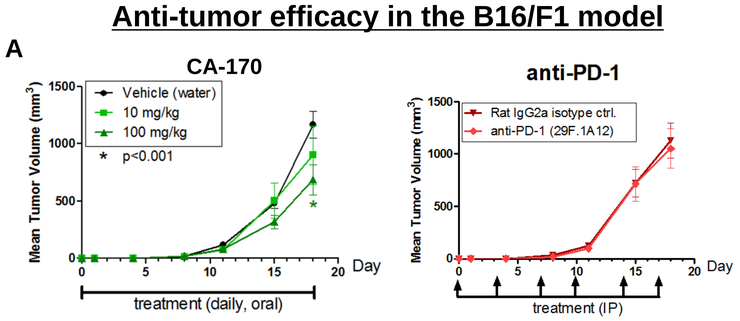
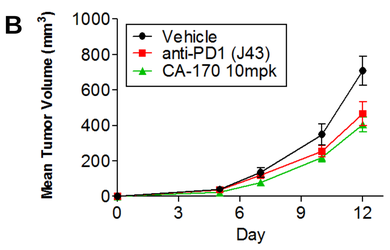


Anti-tumor efficacy in the MC38 model

B



A) Mice implanted with subcutaneous B16F1 tumor cells were treated as indicated. Tumor growth inhibition at Day 18 is 23%, 41% and 7% for CA-170 at 10 mg/kg, CA-170 at 100 mg/kg and anti-PD-1 (100 µg/day), respectively. **B)** MC38 tumor cells were subcutaneously implanted in C57BL/6 mice on Day 0 and dosed on Day 1 with vehicle (water, PO; n=10), CA-170 (PO; n=10) or anti-PD-1 (IP, Q7D; n=10). Tumor growth inhibition at Day 13 was 43% and 36% for CA-170 and anti-PD-1, respectively.

Increased peripheral T cell activation

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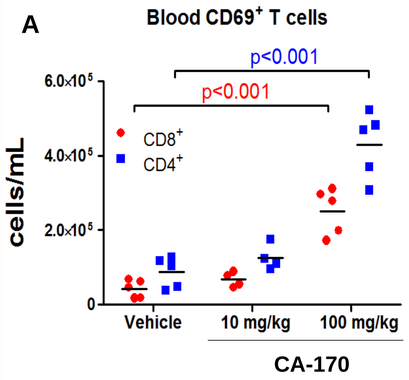

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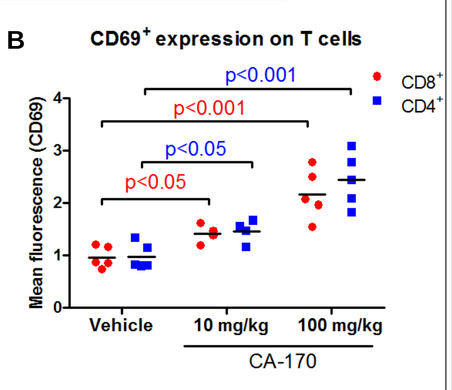

Increased tumor infiltrating T cell activation

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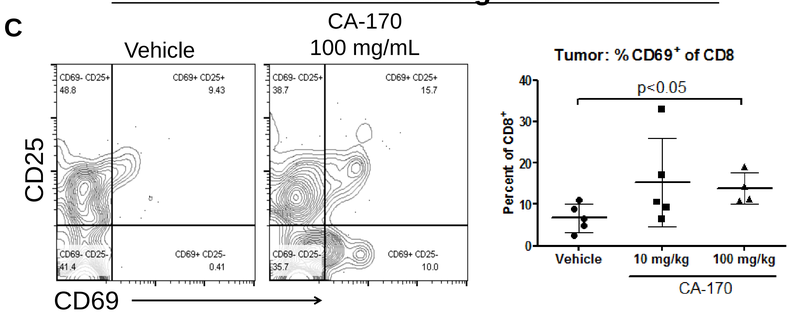
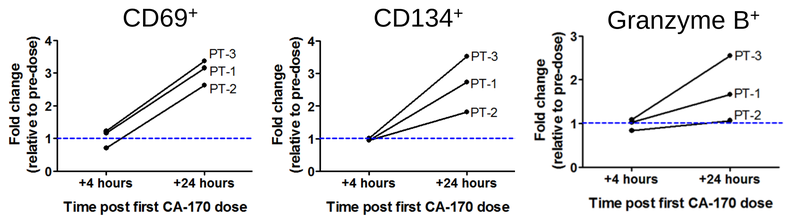


C57BL/6 mice were subcutaneously implanted with B16/F1 tumor cells, randomized and assigned to one of three indicated treatment groups (n=5/group). **A)** The number of $CD69^+$ peripheral blood T cells and **B)** CD69 expression level were analyzed following 2 days of oral CA-170 dosing. **C)** Tumor infiltrating $CD8^+$ T cells were analyzed following 6 days of oral dosing. P-values were determined by Student's t-tests

Evidence of CA-170 immune PD activity in human peripheral blood (NCT02812875)

Change in the percent of circulating $CD8^+$ T cells expressing:



Peripheral blood (drawn pre-, 4 hours post and 24 hours post CA-170 dosing) from patients dosed orally at 50 mg (PT-1; n=1), 100 mg (PT-2; n=1) or 200 mg (PT-3; n=1). The blue dashed line represents the pre-dosed patient sample.

Summary

- ❖ CA-170 is the first potent and selective, oral immune checkpoint antagonist to be tested in human cancer patients.
- ❖ Non-clinical data demonstrates dose-dependent oral exposure, immune modulation and anti-tumor activity.
- ❖ Based on the non-clinical CA-170 exposure and pharmacodynamic data in mice, the clinical CA-170 starting dose of 50 mg shows sufficient drug exposure to potentially elicit biological activity in humans.

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