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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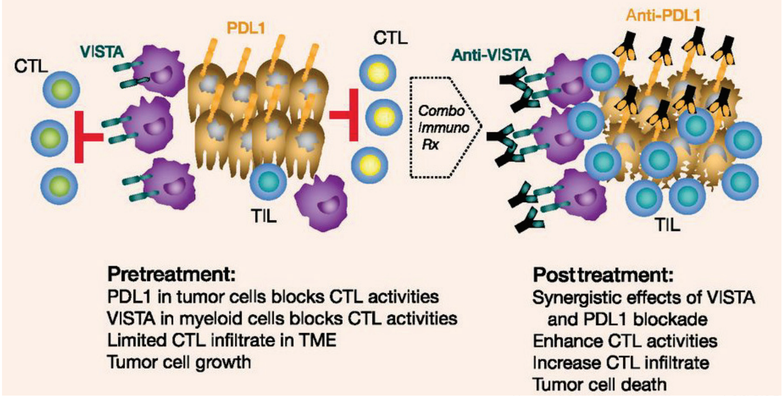
Introduction

- The programmed-death 1 (PD-1)/programed death ligand 1 (PD-L1) and V-domain Ig suppressor of T-cell activation (VISTA) pathways are functionally independent immune checkpoints that negatively regulate T-cell function and regulate 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).

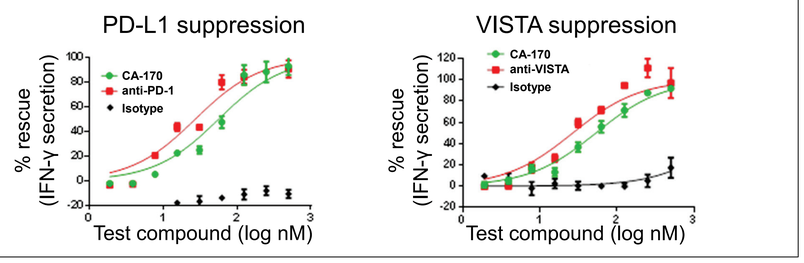
Tailored approach for tumors expressing PD-L1 and VISTA in TME



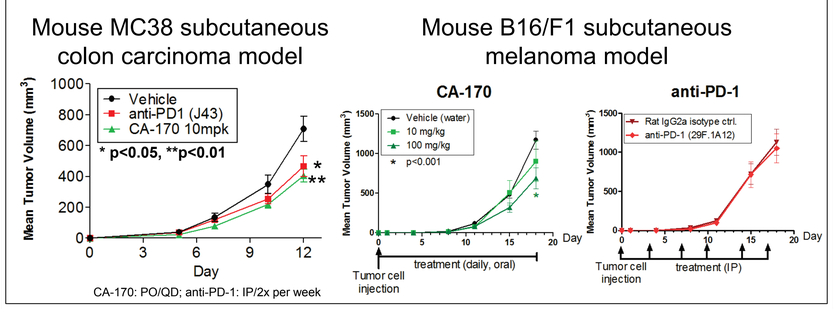
Lines, et al, 2014, Cancer immunology research;2(6):510-7

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

In Vitro Rescue of Suppressed Human T Cell Effector Function

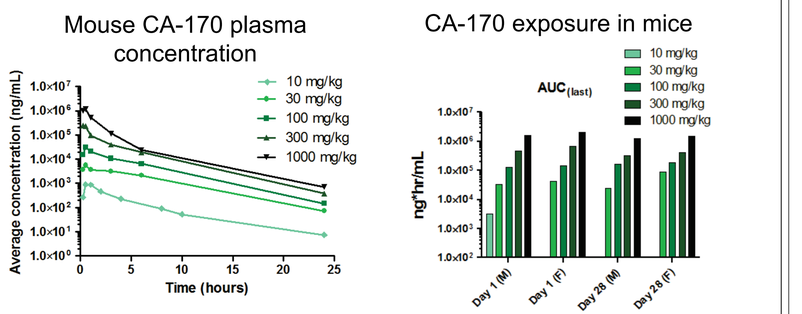


In Vivo Anti-tumor Efficacy



CA-170: PO/QD; anti-PD-1: IP/2x per week

Oral Bioavailability



	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**

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 of the tumor to an 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 recommended 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 (SSCHN)*
Secondary	➢ To assess the pharmacokinetic **(PK) profile** ➢ To assess the preliminary **anti-cancer activity**
Exploratory	➢ 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

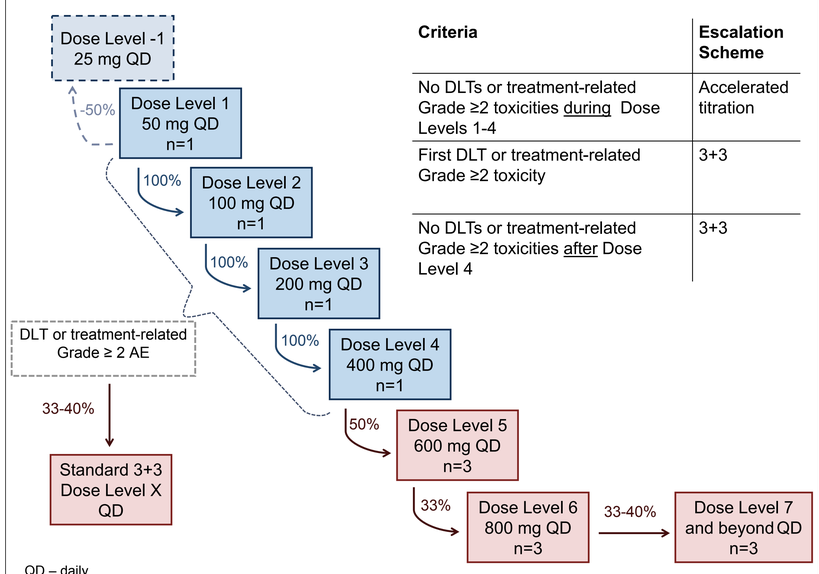
Study Design

Phase 1 first-in-human, open-label study evaluating CA-170 in patients with advanced solid tumors or lymphoma

➢ **Treatment**
- Patients will receive daily oral CA-170 continuously in 21-day cycles

➢ **Phase 1a: Dose Escalation**
- ~50 patients with advanced solid tumors or lymphoma will be enrolled
- Enrollment will initially follow accelerated titration and subsequently switch to a traditional 3+3 design
- Additional patients may be enrolled onto previously explored escalation dose levels to better understand the PK, pharmacodynamic immune effects, and anti-tumor activity of those dose levels

Figure 4. Patient Enrollment – Dose Escalation



Criteria	Escalation Scheme
No DLTs or treatment-related Grade ≥2 toxicities during Dose Levels 1-4	Accelerated titration
First DLT or treatment-related Grade ≥2 toxicity	3+3
No DLTs or treatment-related Grade ≥2 toxicities after Dose Level 4	3+3

QD – daily
Blue = accelerated titration; Red = 3+3 design; %= percent increase from previous dose

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 SSCHN*.

Key Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
Age ≥ 18 years	Known symptomatic CNS involvement
Radiological evidence of measurable disease	Recent anticancer therapy or experimental therapy
ECOG performance status ≤ 1	Other concomitant malignancy
Phase 1a: Histopathologically confirmed unresectable, advanced or metastatic solid tumors or lymphomas; standard therapy, approved anti-PD-1/L1 therapy, does not exist, is unavailable, is ineffective, or patient is not eligible/expected to derive benefit ➢ Anti-PD-1/L1 pre-treated OR naïve	Active autoimmune disease or uncontrolled serious cardiovascular disease or serious infection
Phase 1b: Histologically confirmed unresectable, advanced or metastatic tumors responsive to anti-PD-1/L1 checkpoint inhibitors and/or known to express PD-L1 or VISTA ➢ Anti-PD-1/L1 pre-treated OR naïve	Immunosuppressive therapy, except for ≤ 10 mg/kg/day prednisone or equivalent

ECOG – Eastern Cooperative Oncology Group; HL – Hodgkin lymphoma; NSCLC – non-small cell lung cancer; RCC – renal cell carcinoma; SSCHN – head and neck squamous cell carcinoma; UC – urothelial carcinoma

Study Status

- This study was initiated in June 2016
- As of 05 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

Gao, J., Ward, J.F., Pettaway, C.A., Shi, L.Z., Subudhi, S.K., Vence, L.M., Zhao, H., Chen, J., Chen, H., Efstathiou, E., et al. (2017). VISTA is an inhibitory immune checkpoint that is increased after ipilimumab therapy in patients with prostate cancer. Nat. Med. *advance online publication*.

Koyama, S., Akbay, E.A., Li, Y.Y., Herter-Sprie, G.S., Buczkowski, K.A., Richards, W.G., Gandhi, L., Redig, A.J., Rodig, S.J., Asahina, H., et al. (2016). Adaptive resistance to therapeutic PD-1 blockade is associated with upregulation of alternative immune checkpoints. Nat. Commun. 7, 10501.

Lazorchak, A.S., Patterson, T.D., Ding, Y., Sasikumar, P., Sudarshan, N., Gowda, N., Ramachandra, R., Samiulla, D., Giri, S., Eswarappa, R., et al. (2016). P219 CA-170, a first in class oral small molecule immune checkpoint antagonist, promotes T cell immune activation and inhibits tumor growth in pre-clinical models of cancer. J. Immunother. Cancer 4, 73.

Lines, J.L., Sempere, L.F., Broughton, T., Wang, L., and Noelle, R. (2014). VISTA Is a Novel Broad-Spectrum Negative Checkpoint Regulator for Cancer Immunotherapy. Cancer Immunol. Res. 2, 510–517.

Liu, J., Yuan, Y., Chen, W., Putra, J., Suriawinata, A.A., Schenk, A.D., Miller, H.E., Guleria, I., Barth, R.J., Huang, Y.H., et al. (2015). Immune-checkpoint proteins VISTA and PD-1 nonredundantly regulate murine T-cell responses. Proc. Natl. Acad. Sci. *112*, 6682–6687.

Ribas, A., Puzanov, I., Dummer, R., Schadendorf, D., Hamid, O., Robert, C., Hodi, F.S., Schachter, J., Pavlick, A.C., Lewis, K.D., et al. (2015). Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. Lancet Oncol. *16*, 908–918.

Weber, J.S., Kudchadkar, R.R., Gibney, G.T., Conti, R.C.D., Yu, B., Wang, W., Sarnaik, A., Martinez, A.J., Kroeger, J., Eysmans, C., et al. (2013). Phase I/II trial of PD-1 antibody nivolumab with peptide vaccine in patients naive to or that failed ipilimumab. J. Clin. Oncol. *31*.

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