Phase 1 study of CA-170, a first-in-class, orally available, small molecule immune checkpoint inhibitor (ICI) dually targeting VISTA and PD-L1, in patients with advanced solid tumors or lymphomas

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Introduction

V-domain Ig suppressor of T-cell activation (VISTA) and Programmed-death 1 (PD-1) are independent immune checkpoints that negatively regulate T-cell function1. VISTA is expressed on both immune cells and tumor cells2-4. Most noticeably, strong expression of VISTA in epithelial metastases is strikingly higher than in other solid tumors, has implications for the immune response in this cancer with inhibitors blocking VISTA. Furthermore, VISTA is found to be upregulated in cancers as a potential resistance mechanism after therapy with immune checkpoint inhibitors (ICIs)5-7. As such, it has been considered a target for ICI therapy. Pre-clinical studies demonstrated that dual blockade of both VISTA and PD-L1 can be synergistic1. CA-170 is a first-in-class small molecule oral inhibitor that directly targets VISTA and PD-L1 and has demonstrated anti-tumor activity in multiple preclinical models. This presentation gives an update to the ongoing Phase 1 trial (ClinicalTrials.gov NCT02512675) presented last year. A Phase 2 study is also ongoing8.

Methods and Study Design

CA-170 Phase 1 First-In-Human Dose Escalation Trial (CA-170-101)

- Accelerated trial of 3 cohorts, followed by 3 + 3 design
- Selected dose levels based on pharma-filled patients

Objectives

- Primary: Safety, Recommended Phase 2 Dose (RP2D), and MTD
- Secondary: PK and anti-cancer activity
- Exploratory: biomarkers and PD effects

Patient Population

- Patients with advanced solid tumors or lymphoma for which standard therapy, does not exist, is not available, or is no longer active
- Eligible patients were aged 18 and above who had advanced solid tumors or lymphomas, or adequate organ function, and ECOG PS 0-1.
- Study sites in South Korea, US, Spain, UK

Inclusion:
- Oral, QD or BID, dosing in continuous 21-day cycles

Baseline Disease Characteristics

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<td>Median # of prior therapy</td>
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Baseline Patient Characteristics

- M/F: 56 (44)/13 (16)
- Male: 50 (82.1)
- Median age: 68 (51-79)
- Median ECOG PS: 0 (0-2)
- Baseline performance status was 0 in 39 (88.2) patients and 1 in 5 patients
- Median # of prior therapy used: 3 (Range, 1-7)

Results: Overall Safety Summary

- No DLTs were observed to date. MTD and RP2D have not yet been established.
- The majority of TEAEs and TRAEs were mild/moderate (Gr. 1/2) and self-limiting or resolved with concomitant medications.
- 53% of patients had received prior treatment, 17% patients were new treatment naïve patients.

- No Grade 4 or 5 toxicity was observed.
- The short half-life allows the flexibility to control drug exposure and manage immune-related side effects.
- Serious immune-related events, reported with antibody ICIs, have been milder and reversible with the small molecule approach.
- Signs of immune-modulating effect were also observed in peripheral blood and tumor tissue.

Pharmacokinetics

- Systemic exposure (C₀, Cₚ, AUC₀→∞) increased approximately proportionally with increasing doses for both QD and BID schedules.
- The short half-life allows the flexibility to control drug exposure and manage immune-related side effects.
- Patients showed a trend towards significant therapeutic concentration with more frequent dosing.
- Inter-patient variability was within the expected range, given the potential impacting variables of trial administration, daily dosing and a highly heterogeneous patient population enrolled thus far.

Anti-Tumor Activity Summary

- Overall, 51 patients were evaluable for anti-tumor activity with at least one post baseline restaging.
- 25 pts (50%) showed SD per RECIST with 1 ongoing, 8 demonstrating tumor regression from baseline, 11 pts (21%) received no therapy at all or did not achieve SD during treatment, 4 patients showed progression during treatment.
- CA-170, being the first small molecule oral inhibitor of immune checkpoints, demonstrates rapid absorption, good bioavailability, dose proportionality and an acceptable short half-life.
- The short half-life allows the flexibility to control drug exposure and manage immune-related side effects.
- Serious immune-related events, reported with antibody ICIs, have been milder and reversible with the small molecule approach of CA-170 possibly due to quicker drug elimination after dose interruption.
- CA-170 dose and dosing regimen are being optimized in relevant tumor types prior to initiation of confirmatory clinical development of CA-170 in ongoing evaluation of potentially pharmacologically active BID dose in VISTA expressing tumors, including epithelial mesothelioma which has strikingly higher VISTA expression than other solid tumors9.

Conclusions and Future Directions

The maximum dose is 1200 mg BID, which is considered well tolerated.
- CA-170 has a favorable safety profile with preliminary evidence of anti-tumor activity (5 patients have experienced tumor regression from baseline).
- Examples of immune-mediating effect were also observed in peripheral blood and tumor tissue.
- The short half-life allows the flexibility to control drug exposure and manage immune-related side effects.
- CA-170 dose and dosing regimen are being optimized in relevant tumor types prior to initiation of confirmatory clinical development of CA-170 in ongoing evaluation of potentially pharmacologically active BID dose in VISTA expressing tumors, including epithelial mesothelioma which has strikingly higher VISTA expression than other solid tumors.

Phase 2 study is ongoing in India conducted by our collaborator, Aurigene10.

References


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