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 immunity suppression (human or mouse) mediated by VISTA/PD-1H, PD-L1 or PD-L2 (see tables below).

<table>
<thead>
<tr>
<th>Mouse Splenocytes</th>
<th>Test Compound</th>
<th>Proliferation Rescue (in vitro)</th>
<th>IFNγ Rescue (in vitro)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EC50 (nM)</td>
<td>EC50 (nM)</td>
<td></td>
</tr>
<tr>
<td>CA-170</td>
<td>16.32</td>
<td>16.56</td>
<td>33.79</td>
</tr>
<tr>
<td>Anti-PD-1 antibody (clone J4B)</td>
<td>17.05</td>
<td>10.45</td>
<td>12.59</td>
</tr>
</tbody>
</table>

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<tr>
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<tr>
<td></td>
<td>EC50 (nM)</td>
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<td></td>
</tr>
<tr>
<td>CA-170</td>
<td>40.57</td>
<td>149.0</td>
<td>49.35</td>
</tr>
<tr>
<td>Anti-PD-1 antibody (clone 1138)</td>
<td>18.87</td>
<td>22.78</td>
<td>66.87</td>
</tr>
<tr>
<td>Anti-VISTA antibody (clone 79882)</td>
<td>0.5</td>
<td>628.3</td>
<td></td>
</tr>
</tbody>
</table>

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.
- No AEOAL (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 also includes interim data (Nov/01/2016) from the ongoing CA-170-101 Phase I clinical trial which was obtained after the abstract submission.

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

A) Mice implanted with subcutaneous B16F1 tumor cells were treated as indicated. Tumor growth inhibition at Day 18 was 23%, 41% and 7% for CA-170 at 10 mg/kg, CA-170 at 100 mg/kg and anti-PD-1, 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.

Oral CA-170 pharmacokinetic profile in mice

A) Mouse CA-170 plasma concentration

B) CA-170 exposure in mice

C) Balb/c mice

Dose (mg/kg) | 10 | 30 | 100 | 300 | 1000
---|---|---|---|---|---
T1/2 (hours) | 4.57 | 3.94 | 3.29 | 3.02 | 2.70
Max (hours) | 0.5 | 0.5 | 0.5 | 0.5 | 0.5
Cmax (ng/mL) | 890 | 5572 | 31821 | 261823 | 1793147
AUC last (hr ng/mL) | 3170 | 38668 | 136969 | 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 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.

Oral CA-170 pharmacokinetic profile in humans

A) Human CA-170 plasma concentration

B) CA-170 exposure in humans

C) Balb/c mice

Dose (mg) | 50 | 100 | 200 | 400 | 200
---|---|---|---|---|---
T1/2 (hours) | 8.7 | 9.6 | 5.3 | 12.9 | 7.1
Max (hours) | 7.4 | 4 | 3 | 4 | 7
Cmax (ng/mL) | 412 | 1107 | 1998 | 4100 | 2337
AUC last (hr ng/mL) | 5197 | 11019 | 27488 | 66664 | 33998

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

A) CA-170 plasma concentrations after 1 dose (Day 1) and after 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.

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

- CD69+
- CD134+
- Granzyme B

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.