CX-1158-101: A First-in-Human Phase 1 Study of CB-1158, a Small Molecule Inhibitor of Arginase, as Monotherapy and in Combination with an anti-PD-1 Checkpoint Inhibitor in Patients with Solid Tumors

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Immunosuppression in the Tumor Microenvironment

• Despite the important advances in immunotherapy, a limited number of patients derive significant benefit from checkpoint inhibitors.

• Tumor-infiltrating myeloid cells suppress T-cell and NK cell function and can limit the activity of checkpoint inhibitors.

• Arginase is a key immunosuppressive enzyme secreted by tumor-infiltrating myeloid cells.

• Inhibiting arginase offers a novel strategy to relieve immunosuppression and to enhance checkpoint inhibitor activity.

• CB-1158 is a first-in-class oral arginase inhibitor in a Phase 1 clinical study.
Arginase in Cancer Patients

Arginase-positive myeloid cell infiltrate in tumor tissues

Plasma Arginase

Plasma Arginine

High arginase and low arginine in patient plasma
Arginase-Mediated Immune Suppression in Tumor Microenvironment

Arginase is required for proliferation of activated CD8+ T-cells

Arginase depletes arginine in tumor

MDSC/Neutrophil → Arginase → Low Arginine

T-cell/NK cell
↓ proliferation
↓ TCRζ
↓ IFNγ
CB-1158 Inhibits Arginase and Overcomes T-cell Suppression

**CB-1158** inhibits Arginase and overcomes T-cell suppression.

- **Arginase inhibition** increases arginine.

<table>
<thead>
<tr>
<th>Arginase Assay</th>
<th>CB-1158 IC&lt;sub&gt;50&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arginase 1 (recombinant)</td>
<td>98 nM</td>
</tr>
<tr>
<td>Reversal of neutrophil-mediated T-cell suppression</td>
<td>200 nM</td>
</tr>
</tbody>
</table>

MDSC/Neutrophil → Arginase → **High Arginine** → T-cell/NK cell

↑ proliferation

↑ TCRζ

↑ IFNγ
CB-1158 Has Single Agent and Combination Activity in Syngeneic Tumor Models

**Increased plasma and tumor arginine**

**Plasma**

<table>
<thead>
<tr>
<th>Arginine (µM)</th>
<th><strong>Vehicle</strong></th>
<th><strong>CB-1158</strong> (100 mg/kg single dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>400</td>
</tr>
<tr>
<td>100</td>
<td>200</td>
<td>300</td>
</tr>
<tr>
<td>200</td>
<td>300</td>
<td>400</td>
</tr>
</tbody>
</table>

**Tumor (LLC)**

<table>
<thead>
<tr>
<th>Arginine (mmol/g)</th>
<th><strong>Vehicle</strong></th>
<th><strong>CB-1158</strong> (100 mg/kg single dose)</th>
</tr>
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<td>0</td>
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</tr>
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<td>200</td>
<td>300</td>
<td>400</td>
</tr>
</tbody>
</table>

**Monotherapy anti-tumor activity**

**LLC (Lung)**

- **Vehicle**
- **CB-1158** 100 mg/kg BID

**Increased CD8+ TILs**

**CT26 (Colon)**

- **Vehicle**
- **CB-1158**
- **α-PD-L1**
- **CB-1158 + α-PD-L1**

Combination anti-tumor activity with checkpoint inhibitor

**Tumor Volume (mm³)**

**Days Post Implant**

- **Vehicle**
- **CB-1158**
- **α-PD-L1**
- **CB-1158 + α-PD-L1**
CX-1158-101 Phase 1 Study Objectives

• Primary
  – Evaluate the safety and tolerability of CB-1158 in patients with advanced/metastatic and/or treatment-refractory solid tumors
    • Monotherapy
    • Combination with anti-PD-1 therapy

• Secondary
  – Select the recommended Phase 2 dose (RP2D) of CB-1158
    • Monotherapy
    • Combination with anti-PD-1 therapy
  – Determine the PK of CB-1158
  – Evaluate the anti-tumor effect of CB-1158

• Exploratory
  – Evaluate the pharmacodynamic effects of CB-1158 and identify potential biomarkers
CX-1158-101 Phase 1 Study Design

**Dose Escalation**

- **Monotherapy**
  - All-comer patients with advanced/metastatic solid tumors
  - 3+3 design*
  - PO dosing, BID schedule

- **Anti-PD-1 Combination Therapy**
  - Combo with full dose α-PD-1
  - NSCLC, RCC, melanoma

**Dose Expansion Cohorts**

- NSCLC
- CRC
- SCCHN, RCC, Gastric, Bladder, Melanoma

- Prior α-PD-1/PD-L1 therapy
  - NSCLC
  - Melanoma

  Additional naïve and α-PD-1/α-PD-L1 refractory tumor types under consideration

*Additional patients enrolled into cleared dose levels for biomarker assessments
CX-1158-101 Phase 1 Patient Selection

**Inclusion:**
- Age ≥18
- ECOG PS 0-1
- Adequate renal, hepatic and hematologic function
- Prior PD1/PDL-1 allowed.

**Exclusion:**
- Immunosuppression pred > 10 mg
- Autoimmune disease
- Valproic acid and xanthine oxidase inhibitors

**Dose Levels**
- 600 mg
- 500 mg
- 400 mg
- 300 mg
- 225 mg
- 150 mg
- 100 mg
- 50 mg
CX-1158-101 Phase 1 Study Assessments

• Safety
  – Standard adverse event (CTCAE) and laboratory monitoring
  – Markers of urea cycle inhibition (plasma ammonia, BUN)

• PK, pharmacodynamics and biomarkers
  – Plasma drug concentration
  – Plasma arginine and arginase activity
  – Arginase expression and immune modulation in the periphery and tumor
  – Urinary orotic acid

• Tumor response
  – Standard RECIST and immune-related RECIST criteria
Urinary Orotic Acid is a Sensitive Biomarker to Monitor Urea Cycle Inhibition

- Arginase is also a urea cycle enzyme
  - “Sequestered” location in hepatocytes
  - Therapeutic window observed in preclinical species
- Urinary orotic acid is a highly sensitive biomarker of urea cycle function
- Urinary orotic acid is being measured in this Phase 1 study
  - Elevations above 5x ULN triggers further evaluation of that dose level

### Table: Arginase Function and CB-1158 IC\textsubscript{50}

<table>
<thead>
<tr>
<th>Arginase Function</th>
<th>CB-1158 IC\textsubscript{50}</th>
</tr>
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<tbody>
<tr>
<td>Immunosuppression</td>
<td>0.2 µM</td>
</tr>
<tr>
<td>Urea cycle</td>
<td>260 µM</td>
</tr>
</tbody>
</table>

### Graph: Urinary orotic acid (µmol/mmol Cr)

- Inherited urea cycle defect (severe symptoms, elevated ammonia)
- Healthy carriers of urea cycle defect (no clinical impact, normal ammonia)
## Study Demographics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>N=17*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [median (range)]</td>
<td>61 (49-77)</td>
</tr>
<tr>
<td>Female/Male [N (%)]</td>
<td>12 (71)/5 (29)</td>
</tr>
<tr>
<td>CB-1158 Dose [N]</td>
<td></td>
</tr>
<tr>
<td>50 mg BID</td>
<td>8^</td>
</tr>
<tr>
<td>100 mg BID</td>
<td>6</td>
</tr>
<tr>
<td>150 mg BID</td>
<td>3</td>
</tr>
<tr>
<td>Prior systemic regimens</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>4 (1-11)</td>
</tr>
<tr>
<td>Prior α-PD-1/α-PD-L1 [N (%)]</td>
<td>5 (29)</td>
</tr>
<tr>
<td>ECOG [N (%)]</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2 (12)</td>
</tr>
<tr>
<td>1</td>
<td>15 (88)</td>
</tr>
</tbody>
</table>

*Data cut: April 24, 2017

^Additional patients enrolled for biomarker assessments
Time on Study

17 patients enrolled with 7 ongoing*

*Data cut: April 24, 2017
## Safety: Treatment-Related Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Total [N (%)]</th>
<th>≥Grade 3 [N (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with Any AE</td>
<td>3 (18)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1 (5.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (5.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Increased AST</td>
<td>1 (5.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1 (5.9)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

- No drug-related SAEs
- Reversible elevations of urinary orotic acid above 5X ULN threshold at 150 mg dose level (2 of 3 patients)
  - Patients asymptomatic without other evidence of urea cycle inhibition
  - Levels comparable to healthy heterozygous carriers for urea cycle defects
  - Additional evaluation of 150 mg dose level ongoing

*Data cut: April 24, 2017*
Pharmacokinetics

<table>
<thead>
<tr>
<th>Cohort (N)</th>
<th>$T_{1/2}$ (C1D1) (hr)</th>
<th>$C_{\text{max}}$ (C1D15) (µM)</th>
<th>$C_{\text{min}}$ (C1D15) (µM)</th>
<th>$AUC_{t}$ (C1D15) (µM*hr)</th>
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<tr>
<td>50 mg BID (5^)</td>
<td>6.2 ± 1.0</td>
<td>3.3 ± 0.5</td>
<td>1.6 ± 0.6</td>
<td>30.2 ± 6.5</td>
</tr>
<tr>
<td>100 mg BID (6^)</td>
<td>6.0 ± 0.6</td>
<td>8.4 ± 1.4</td>
<td>4.1 ± 0.5</td>
<td>80.6 ± 12.2</td>
</tr>
<tr>
<td>150 mg BID (3)</td>
<td>5.0 ± 0.5</td>
<td>9.9 ± 2.4</td>
<td>4.4 ± 0.8</td>
<td>85.5 ± 7.6</td>
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^N=4 for steady state values on C1D15
Pharmacokinetics

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<tbody>
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<td>50 mg BID (5(^\wedge))</td>
<td>6.2 ± 1.0</td>
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\(^{\wedge}N=4\) for steady state values on C1D15

- Six hour half-life:
  - Supports BID dose schedule
  - Consistent with renal clearance predicted from preclinical studies
Pharmacokinetics

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\(^\wedge\)N=4 for steady state values on C1D15

- Steady state trough levels above the IC_{90} for arginase inhibition at all dose levels
CB-1158 Inhibits Arginase in Patient Plasma

Pre-dose Plasma Arginase

Post-dose Plasma Arginase Activity

Arginase Activity (μM \text{13C-ornithine/h})

C1D1 pre-dose
C1D1 6 hr post-dose
C1D15 pre-dose

peak
steady state trough

95% inhibition (N=11)
90% inhibition (N=7)

50 mg
100 mg

0.0 0.5 1.0 1.5 2.0

Healthy Donors Patients on study (pre-dose)
CB-1158 Increases Arginine in Patient Plasma

Pre-dose Plasma Arginine

Post-dose Plasma Arginine

Arginine Levels

Arginine (fold change)

Healthy Donors  Patients on study (pre-dose)

Arginine (μM)

0 25 50 75 100 125 150

50 mg 100 mg 150 mg

C1D1 C1D15

1 2 3 4 5 6 7

1.5X
Immune Biomarkers: Peripheral Blood

**Increased PD-1\(^+\) T-cells**

- **CD4\(^+\)/FoxP3\(^-\)**
  - C1D1
  - C2D1
  - *\(p<0.05\)

- **CD8\(^+\)**
  - C1D1
  - C2D1
  - *\(p<0.05\)

**Increased CD3\(\zeta\) on cytokine-producing NK cells**

- C1D1
- C2D1
- *\(p<0.05\)

Sub-populations and activation state of T-cells and NK cells by flow cytometry
Conclusions

• CB-1158 is a first-in-class, potent, selective arginase inhibitor
• Oral dosing of CB1158 was well tolerated at all doses tested
• Steady state trough exposure >IC$_{90}$ for arginase, with 90-95% arginase inhibition and increases in plasma arginine
• Preliminary evidence of peripheral immune modulation - to be further explored
• Ongoing Phase 1 study will continue to explore monotherapy as well as the combination with anti-PD-1 therapy in a variety of solid tumor indications
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Yonchu Jenkins, Ph.D.
Mark Bennett Ph.D.

Incyte Collaborators
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Howard Kallender, Ph.D.

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