A Phase I Study of an Agonist Anti-CD27 Human Antibody (CDX-1127) in Patients with Advanced Hematologic Malignancies or Solid Tumors
Early Data from Ongoing Dose-Escalation in Hematologic Malignancies

Ansell, Stephen1; Northfelt, Donald2; Flinn, Ian3; Burris, Howard3; Dinner, Shira4; Villalobos, Victor3; Sikic, Branimir5; Pilja, Lana6; Yellin, Michael6; Keler, Tibor6; Davis, Thomas6

CDX-1127: A fully human mAb to CD27
- CD27 is a potent co-stimulatory molecule that drives T cell activation and survival through interaction with CD70.
- CDX-1127 is an agonist anti-CD27 IgG1 mAb that induces activation and proliferation of human T cells when combined with T-cell receptor stimulation.
- CDX-1127 has been shown effective in murine tumor models alone, and now in combination with chemotherapy or checkpoint inhibitors (poster 85).
- CD27 can be expressed at high levels on lymphoma and leukemia cells, presenting a target for direct anti-tumor effects.
- CDX-1127 promotes antibody-dependent cell-mediated cytotoxicity of lymphoma cells and has potent anti-tumor effects in xenograft models of human lymphoma cell lines.
- In hematologic malignancies, CDX-1127 may induce anti-tumor activity by both immune activation and direct effector function.

Phase 1 Clinical Study Design
- Two study arms: Hematologic Malignancies and Solid Tumors (poster 146)
- Hematologic malignancy eligibility:
  - Chronic lymphocytic leukemia
  - Burkitt's lymphoma
  - Mantle cell lymphoma
  - Marginal zone B cell lymphoma
  - Progressive disease subsequent to previous therapies; no remaining approved therapy options
  - Washout from prior therapies including:
    - ≥4 weeks for chemotherapy (or 5 half-lives, if longer), monoclonal based therapies and systemic radiation
    - ≥2 weeks for all other immunotherapy
- Standard 3+3 dose-escalation (0.1, 0.3, 1, 3 or 10 mg/kg)
- Weekly dosing to establish safety with maximum exposure
- Potential for subsequent malignancy-specific expansion cohorts to further characterize activity of CDX-1127.

Dose-Escalation Phase Results To Date
- Seventeen patients have been treated with CDX-1127 from 0.1 to 3 mg/kg.
- The final dose level (10 mg/kg) is open to accrual.

Baseline Patient Characteristics (n=17)

<table>
<thead>
<tr>
<th>Age, years [median (range)]</th>
<th>63 (23-92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male [n(%)]</td>
<td>12 (71%)</td>
</tr>
<tr>
<td>ECOG Performance Status [n (%)]</td>
<td>5 (29%)</td>
</tr>
</tbody>
</table>
| Tumor Types [n (%)]
  - Diffuse large B-cell       | 8 (47%)   |
  - Follicular                  | 4 (24%)   |
  - Hodgkin                     | 3 (18%)   |
  - Marginal zone               | 1 (6%)    |
  - Non-hodgkin B-cell, NOS     | 1 (6%)    |
| Stage at Study Entry [n (%)]
  - I                         | 2 (12%)   |
  - II                        | 1 (6%)    |
  - III                       | 3 (18%)   |
  - IV                        | 11 (65%)  |
| Duration of Disease, years [median (range)] | 5.3 (0.7-26.9) |
| Lines of treatment [median (range)]
  - Anticancer therapy         | 4.0 (1-12) |
  - Cytotoxic chemotherapy      | 3.0 (1-9)  |
| Prior treatments received [n (%)]
  - Radiation                  | 8 (47%)   |
  - Autologous Transplant       | 7 (41%)   |

Safety
- No DLT, treatment-related SAEs, or toxicity resulting in discontinuation of CDX-1127 reported to date

Treatment-Related Adverse Events (n=12)

<table>
<thead>
<tr>
<th>CTCAE Grade 1</th>
<th>CTCAE Grade 2</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>3 (25%)</td>
<td>3 (25%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>3 (25%)</td>
<td>3 (25%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>3 (25%)</td>
<td>3 (25%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (25%)</td>
<td>3 (25%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2 (17%)</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>Blood alkaline phosphatase increased</td>
<td>2 (17%)</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>2 (17%)</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (17%)</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 (8%)</td>
<td>1 (8%)</td>
</tr>
</tbody>
</table>

Adverse Event data has been reported for twelve patients treated with CDX-1127 from 0.1 to 1 mg/kg. Table does not include grade 1 adverse events that occurred in one patient.

Pharmacokinetics and Immune Monitoring
- Pending analyses:
  - Flow cytometry on PBMC
  - Serum cytokine and chemokine levels
  - Gene expression profiling on PBMC
- Preliminary analysis shows no significant depletion of T cells

Conclusions:
- CDX-1127 (through 3 mg/kg) has been well-tolerated with minimal toxicity in patients with B cell lymphoma
- Immune activation data are pending. Preliminary analysis shows no significant change in circulating T cell levels
- Anti-lymphoma activity is supported by a Complete Response seen in a patient with heavily pretreated Hodgkin Disease
  - Activity data for the 3 and 10 mg/kg cohorts are pending
- The combined safety and activity data from the hematologic and solid tumor arms of this phase 1 study strongly support the further development of CDX-1127, particularly in combination therapy.