Improved Outcomes in Allogeneic Hematopoietic Cell Transplant Patients Treated with Brincidofovir (CMX001, BCV) for Disseminated Adenovirus Disease Compared to Literature: Updated Preliminary Results from the AdVise (CMX001-304) Study

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Disclosure Statement

• Michael Grimley, MD, Associate Professor of Clinical Pediatrics, Bone Marrow Transplant and Immune Deficiency, Cincinnati Children's Hospital Medical Center
  – No disclosures
Adenovirus: Epidemiology and Current Treatment Options

• Wide spectrum of presentation from asymptomatic viremia to severe and often disseminated disease
• Allogeneic (allo) HCT recipients at greatest risk
• Mortality reported to be up to 80% for allo HCT recipients with disseminated AdV disease*
• 5 to 50% incidence of infection in allo HCT recipients
  – Dependent on risk factors such as young age, receipt of T cell-depleted graft, mismatched or unrelated graft, cord blood, acute graft versus host disease, etc.
• Current standard of care: supportive, reduction of immune suppression, and unproven antivirals, typically IV cidofovir (CDV) despite risk of significant renal injury

High Short-term Mortality with Disseminated AdV Disease

Greater than 60% short-term mortality reported in a prospective, single center study in pediatric patients (Lion 2003)

Compartment AdV PCR positive, blood AdV PCR negative

Any blood AdV PCR positive (N = 36, 33 with disseminated disease; < 40% survival ~ 120 days after first AdV positivity)

Adapted from Lion T, et al. Blood 2003;102(3):1114-20
Brincidofovir (BCV, CMX001)

- BCV is a lipid-conjugate of CDV, administered orally twice-weekly (BIW)
- In Phase 3 clinical development for prevention of cytomegalovirus (CMV) in allo HCT recipients and treatment of AdV
- Also in development as possible medical countermeasure for smallpox (under Animal Rule)
- *In vitro* activity against multiple dsDNA viruses
- Preliminary data from Phase 3 AdVise trial (N = 48 subjects) presented at IDSA/IDWeek September 2014*

*Young et al. ID Week 2014 Abstracts, Late Breaker Oral Abstract LB-3, Open Forum Infect Dis (Fall 2014) 1 (suppl 1): S66-9*
Safety Database of > 1000 Individuals To Date

- Lack of hematologic toxicity allows pre-engraftment dosing
- No nephrotoxicity; not a substrate of kidney human organic anion transporter 1 (hOAT 1)
- Drug-related GI events manageable and not dose-limiting
- Non-adverse low-level ALT (SGPT) elevation observed in preclinical testing, without histopathology
- Asymptomatic elevations in serum aminotransferases manageable and not dose-limiting
AdVise: Study Overview

- All subjects receive 12 wks of open-label treatment with BCV 100 mg BIW (or 2 mg/kg BIW if weight < 50 kg)

- Rescue BCV therapy (up to 12 additional wks treatment) available for relapse during follow-up
AdVise: Prospectively Defined Cohorts

**Cohort A:** Allo HCT patients “at risk of AdV disease progression”
(EITHER asymptomatic with plasma AdV ≥ 1000 c/mL OR symptomatic in one organ system and plasma AdV < 1000 c/mL)

**Cohort B:** Allo HCT patients with “disseminated AdV disease”
(EITHER symptomatic in one organ system with plasma AdV ≥ 1000 c/mL OR symptomatic in two or more organ systems)

**Cohort C:** All other patients
(Solid organ transplant recipients, chemotherapy patients, etc. with disseminated AdV disease or at risk of AdV disease progression as defined for Cohorts A and B)

Cohort A: 18 (21%)
Cohort B: 54 (64%)
Cohort C: 13 (15%)
<table>
<thead>
<tr>
<th>Demographic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (Range)</td>
<td>12 yrs</td>
</tr>
<tr>
<td></td>
<td>(8 mos to 69 yrs)</td>
</tr>
<tr>
<td>Age &lt; 18 yrs (n [%])</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>(63%)</td>
</tr>
<tr>
<td>Male Sex (n [%])</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>(67%)</td>
</tr>
<tr>
<td>White or Caucasian Race (n [%])</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>(74%)</td>
</tr>
</tbody>
</table>
• Median date treatment initiated after HCT = 77 days (range: -1 to 2236)

• Median absolute lymphocyte count = 0.35 K/µL (range: 0 to 2.47; n = 36*)

• One third (18 of 54) had ongoing GvHD at enrollment
  – Including 19% (10 / 54) with GvHD of intestine

• Prior treatment with IV CDV reported in 41% (22 / 54)

* Centralized safety laboratory reporting not available at study initiation; TLTC (too low to count) values imputed as zero
AdVise: Reason for Transplant (Cohort B)

Reason for Transplant

- Acute lymphocytic leukemia: 20%
- Acute myelogenous leukemia: 20%
- Congenital immunodeficiency: 13%
- Myelodysplasia: 7%
- Aplastic anemia: 4%
- Multiple myeloma: 4%
- Other: 32%
AdVise: HCT Graft Source & Donor Type (Cohort B)

**HCT Graft Source**
- **Cord Blood**: 24%
- **Peripheral Blood Stem Cell**: 41%
- **Bone Marrow**: 31%
- **Other**: 4%

**Donor Type**
- **Matched unrelated**: 63%
- **Haploidentical**: 13%
- **Mismatched**: 9%
- **Matched related**: 9%
- **Other or Unknown**: 6%
- **Other**: 4%

(Coverage Image from Cincinnati Children's Hospital Medical Center)
AdVise: Graft Manipulation & Preparation Regimen (Cohort B)

Graft Manipulation

- T cell depletion and/or CD34+ selection: 26%
- ATG or Campath: 74%

Preparation Regimen

- Myeloablative: 57%
- Reduced intensity: 35%
- Other or Unknown: 8%
• Median plasma AdV viremia at baseline: $4.5 \log_{10}$ copies/mL (range: not detected to 7.6)
AdVise: Co-infection with Other dsDNA Viruses (Cohort B)

**Subjects Co-infected with AdV and Other dsDNA Viruses**

- 1 other dsDNA virus: 43%
- 2 other dsDNA viruses: 19%
- 3 other dsDNA viruses: 2%

**Other dsDNA Virus Co-infections**

- BK virus: 46%
- Cytomegalovirus: 31%
- Epstein-Barr virus: 7%
As of 8 January 2015, data available from 85 subjects
  – 54 allo HCT recipients with disseminated AdV disease enrolled in Cohort B across 17 study centers

Median 11 weeks of follow-up (range: 1-34)

Median treatment duration: 39 days (range: 1-167) or 12 doses (range: 1-48)
  – Treatment extended for > 12 wks in 7 subjects
AdVise: Virologic Responses in Disseminated AdV Disease (Cohort B; N = 50*)

<table>
<thead>
<tr>
<th>Description</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with plasma AdV undetectable any time on treatment (n [%]):</td>
<td>29 (58%)</td>
</tr>
<tr>
<td>Subjects with plasma AdV undetectable at end of treatment (n [%]):</td>
<td>23 (46%)</td>
</tr>
<tr>
<td>Median (range) time to minimum plasma AdV on treatment (days):</td>
<td>15 (3 to 106)</td>
</tr>
<tr>
<td>Subjects with $\geq 3 \log_{10}$ copies/mL decrease or to undetectable (n [%]):</td>
<td>33 (66%)</td>
</tr>
</tbody>
</table>

* Subjects with detectable plasma AdV viremia at baseline
# AdVise: Change in Plasma AdV Viremia on Treatment (Cohort B)

## Mean Change from Baseline Plasma AdV Viremia On Treatment (Cohort B; N = 50*)

<table>
<thead>
<tr>
<th>Time on Treatment</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>50</td>
</tr>
<tr>
<td>Day 4</td>
<td>39</td>
</tr>
<tr>
<td>Week 1</td>
<td>44</td>
</tr>
<tr>
<td>Week 2</td>
<td>38</td>
</tr>
<tr>
<td>Week 3</td>
<td>35</td>
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<tr>
<td>Week 4</td>
<td>29</td>
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<tr>
<td>Week 6</td>
<td>26</td>
</tr>
<tr>
<td>Week 8</td>
<td>21</td>
</tr>
<tr>
<td>Week 10</td>
<td>16</td>
</tr>
<tr>
<td>Week 12</td>
<td>13</td>
</tr>
</tbody>
</table>

* Subjects with detectable plasma AdV viremia at baseline
AdVise: Clearance of AdV from Body Compartments

Percent Clearance by Body Compartment (Any Time on Treatment)

- Plasma: 68%
- Urine: 57%
- Stool: 53%
- Respiratory secretions: 70%
AdVise: Encouraging Short-term Survival in Allo HCT with Disseminated AdV Disease (Cohort B)

Survival in Cohort B: 34 of 54 (63%) allo HCT recipients with disseminated AdV disease with median follow-up of 85 days for living subjects.
• Among 20 deaths reported in Cohort B, none of the fatal adverse events (AEs) was assessed as related to BCV

• Among 7 subjects in Cohort B who were discontinued from BCV due to AE(s), only one event (Grade 2 abdominal pain in one subject) was assessed as related to BCV
Among 54 subjects enrolled in Cohort B with disseminated AdV disease to-date:

- 37% mortality after median follow-up of 75 days
  - compares to literature rates of up to 50 to 80% mortality

- Majority had $\geq 3 \log_{10} \text{c/mL}$ decline or undetectable AdV in plasma, and cleared AdV from respiratory, GI, or genitourinary compartments

- Only one subject discontinued therapy due to a BCV-related event (Grade 2 abdominal pain)

- Almost two-thirds (63%) of subjects co-infected with one or more other (non-AdV) dsDNA viral infections at study entry
What Next for the AdVise Trial?

- Target enrollment in AdVise (CMX001-304) increased to ~ 200 patients (minimum 100 allo HCT with disseminated AdV disease)

- Survival and other outcomes in allo HCT in AdVise to be compared to historical outcomes in matched control patients from same medical centers (Study CMX001-305)

- Epidemiology of AdV and other dsDNA viruses (BKV, CMV, EBV, HHV-6, etc.) will be determined from banked samples at selected centers
The authors are grateful to the study participants and their families and to the following study centers (investigators):

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