Dedicated to Preventing and Treating Life-Threatening Viral Infections

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Adenovirus (ADV) Virologic Response to Brincidofovir in Patients with Evidence of Resistance
Adenovirus: Epidemiology and Treatment Options

- Allogeneic hematopoietic cell transplant (allo HCT) recipients are at greatest risk of severe disease, but AdV infection is a potential issue in any significantly immunosuppressed patient.
- Mortality reported to be up to 80% for allo HCT recipients with disseminated disease.
- 5 to 50% incidence of reported infection in allo HCT appears to be dependent on multiple risk factors (age, graft type, unrelated graft, etc.).
- Current standard of care: supportive, reduction of immune suppression, and unproven antivirals (typically IV cidofovir).

Brincidofovir Mimics Natural Phospholipids

PC
LPC
BCV
Brincidofovir (BCV, CMX001)

- Active against all five families of dsDNA viruses *in vitro*
- Oral delivery
- No evidence of kidney or bone marrow toxicity in > 1,000 subjects receiving BCV
- Completed clinical trials:
  - HALT for AdV preemption
  - CMX001-201 for CMV prevention in HCT
- Ongoing clinical trials:
  - SUPPRESS for CMV prevention in HCT
  - AdVise for AdV treatment in immunocompromised patients
  - Animal efficacy studies for smallpox (biodefense)
BCV Inhibits Adenovirus (AdV) Replication \textit{In Vitro}

<table>
<thead>
<tr>
<th>Adenovirus Serotype</th>
<th>BCV EC_{50} (μM)</th>
<th>CDV EC_{50} (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AdVA31</td>
<td>0.020</td>
<td>1.4</td>
</tr>
<tr>
<td>AdVB7</td>
<td>0.020</td>
<td>1.3</td>
</tr>
<tr>
<td>AdVC1</td>
<td>0.006</td>
<td>N.D.</td>
</tr>
<tr>
<td>AdVD8</td>
<td>0.027</td>
<td>1.0</td>
</tr>
<tr>
<td>AdVE4</td>
<td>0.007</td>
<td>N.D.</td>
</tr>
<tr>
<td>AdVF40</td>
<td>0.006</td>
<td>N.D.</td>
</tr>
</tbody>
</table>

- BCV is active \textit{in vitro} against all AdV species tested and 37 to 70-fold more active than CDV \textit{in vitro}
## Fold Change in EC$_{50}$ against BCV and CDV with BCV and CDV-Resistant Isolates Selected *In vitro*

<table>
<thead>
<tr>
<th>Mutant / Source</th>
<th>AdVC5</th>
<th>Fold Change In EC$_{50}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>BCV</td>
</tr>
<tr>
<td>AdVC5</td>
<td>Wild-type</td>
<td>1.0</td>
</tr>
<tr>
<td>BCV p5$^a$</td>
<td>V303I$^b$</td>
<td>2.2</td>
</tr>
<tr>
<td>BCV p15$^a$</td>
<td>T87I, V303I$^b$</td>
<td>6.0</td>
</tr>
<tr>
<td>CDV p15$^c$</td>
<td>T1151I</td>
<td>4.5</td>
</tr>
<tr>
<td>CDV-R1$^d$</td>
<td>F882L/S1183R</td>
<td>5 - 10</td>
</tr>
<tr>
<td>CDV-R4$^d$</td>
<td>V303I, F882I</td>
<td>8.1</td>
</tr>
<tr>
<td>CDVR5$^d$</td>
<td>A501E, L677F</td>
<td>8.7</td>
</tr>
</tbody>
</table>

$^a$ Resistant mutant selected in the presence of BCV at Chimerix. $^b$ Plaque purified virus. $^c$ Resistant mutant selected in the presence of CDV at Chimerix. $^d$ Data from Kinchington mutant R5, ND – not determined
HALT and AdVise Trials

**HALT**
- Hematopoietic stem cell transplant (HCT) recipients with asymptomatic AdV viremia (≥ 100 DNA copies/mL) stratified based on absolute lymphocyte count at screening (ALC; < 300 or ≥ 300 cells/mm³)
- Randomized to once-weekly (QW) BCV, twice weekly (BIW) BCV, or placebo

**AdVise**
- Open-label oral dosing for 12 weeks: 100 mg BIW or 2 mg/kg BIW if < 50 kg
- **Cohort A**: Allo HCT patients with asymptomatic or single-organ AdV disease
- **Cohort B**: Allo HCT patients with disseminated AdV disease
- **Cohort C**: Other (i.e., non-allo HCT) immunocompromised patients with disseminated AdV disease or limited AdV disease (as defined for Cohorts A and B)
Selection Criteria for AdV Polymerase Genotyping

- Subjects with detectable plasma AdV DNA\(^1\) at the last on-therapy measurement

- Subjects who had virologic breakthrough, defined as:
  - confirmed detectable plasma AdV DNA after confirmed undetectability, or
  - confirmed increase in plasma AdV DNA by \(1 \log_{10}\) after experiencing at least \(1 \log_{10}\) decrease from baseline

\(^1\)ViraCor Laboratories assay, with LLOD of 106 copies/mL
HALT: AdV Viremia During Blinded Treatment

- A greater proportion of subjects randomized to BCV BIW arm achieved undetectable viremia compared to PBO and BCV QW

- Progression to disease or increasing viremia was less common in the BCV BIW group than for the pooled placebo group
HALT Patient with AdV pol Mutation V303I (BCV 100 mg BIW)

*Patient amino acid sequence compared against AdVC5 reference
*Full length pol sequence at baseline was not successful. Alternative amplification of shorter target covering AA283-443 were performed to obtain AA303 sequence.
AdVise: AdV Viremia for First 54 Patients in Cohort B
AdVise: AdV Viremia and AdV pol Genotype for Cohort B Virological Failures

TEM displayed at latest time point tested
NA – data currently not available
NC – no change from baseline
Clearance of AdV Despite Baseline T87I in AdVise Patient

T87I, R317Q, G869S, E1020K
Two mutations were selected in the AdV polymerase following 6 months of passaging with BCV in tissue culture (T87I and V301I); these mutations confer low level BCV resistance *in vitro* (2 to 6-fold).

Analysis of 231 patients receiving BCV for AdV in the HALT and AdVise studies revealed one instance of each mutation

- One patient in HALT developed V303I on therapy associated with virologic failure
- One patient in AdVise had T87I at baseline, but had a complete virologic response by the end of BCV therapy
- Other potential RAMs under evaluation

These results provide genetic evidence for an AdV polymerase mediated mechanism of action for BCV

Current data suggest that adenovirus resistance to brincidofovir will not commonly emerge during therapy and that some patients who have CDV resistant adenovirus may still respond to brincidofovir
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