Emerging CMV Resistance Profile for CMX001

International Conference on Antiviral Research
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Randall Lanier, PhD
Forward-Looking Statements

These slides and the accompanying oral presentation contain forward-looking statements and information. The use of words such as “may,” “might,” “will,” “should,” “expect,” “plan,” “anticipate,” “believe,” “estimate,” “project,” “intend,” “future,” “potential,” or “continue,” and other similar expressions are intended to identify forward looking statements. All of these forward-looking statements are based on estimates and assumptions by our management that, although we believe to be reasonable, are inherently uncertain. Forward-looking statements involve risks and uncertainties, including, but not limited to, economic, competitive, governmental and technological factors outside of our control, that may cause our business, industry, strategy or actual results to differ materially from the forward-looking statements. These statements are also subject to a number of material risks and uncertainties that are described more fully in our filings with the Securities and Exchange Commission, including without limitation our Registration Statement on Form S-1 that was originally filed with the Securities and Exchange Commission on March 8, 2013, and the amendments thereto. Any forward-looking statement speaks only as of its date. We undertake no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events or otherwise, except as required by law.
Disclosures

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CMX001: Novel, Broad Spectrum Antiviral

- Active against all herpesviruses and other dsDNA viruses
- Oral delivery
- No evidence of kidney or bone marrow toxicity
- Long intracellular half-life allows twice-weekly dosing

Enhanced Intracellular Drug Uptake
CMX001 Development Program Advancing in 3 Indications

- **Cytomegalovirus (CMV): Prevention in Hematopoietic Stem Cell Transplant (HSCT) Recipients**
  - Initiating Phase 3 trial SUPPRESS in adult subjects post-HSCT
  - Safety and tolerability in >800 subjects
  - Combination of safety profile (no evidence of kidney or hematologic toxicity) and broad spectrum antiviral activity may enable universal prophylaxis

- **Adenovirus (AdV): Preemptive Therapy in Pediatric and Adult HSCT Recipients**
  - Completed enrollment in Phase 2 trial; data available in 2H 2013

- **Smallpox: Medical Countermeasure for Treatment**
  - Development program based on animal efficacy and human safety
CMX001 Potently Inhibits CMV *In Vitro* (HFF Cells)

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<tbody>
<tr>
<td><strong>CMX001</strong></td>
<td>0.001</td>
<td>0.001</td>
<td>0.003</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>EC₅₀ (µM)</strong></td>
<td></td>
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<td></td>
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<tr>
<td><strong>Ganciclovir</strong></td>
<td>3.8</td>
<td>47</td>
<td>40</td>
<td>43</td>
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<tr>
<td><strong>EC₅₀ (µM)</strong></td>
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<tr>
<td><strong>Cidofovir</strong></td>
<td>0.4</td>
<td>0.8</td>
<td>0.4</td>
<td>16</td>
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<tr>
<td><strong>EC₅₀ (µM)</strong></td>
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HFF = human foreskin fibroblast

Higher Antiviral Levels Inside Cells with CMX001 vs. Cidofovir

CDV-PP formed from 1 μM CDV or CMX001 in HFF cells after 72 hours in culture

CDV-PP in pmoles/million cells

<table>
<thead>
<tr>
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<th>CDV-PP in pmoles/million cells</th>
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<tbody>
<tr>
<td>Cidofovir</td>
<td>0.13</td>
</tr>
<tr>
<td>CMX001</td>
<td>88</td>
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</tbody>
</table>

>600x higher CDV-PP with CMX001

CDV-PP = cidofovir-diphosphate; HFF = human foreskin fibroblast
Source: Chimerix data.
CMX001 Primary CMV Mutation in UL54 Selected *In Vitro*: Impaired Replication, Retained Sensitivity to GCV and FOS

- Wild-type CMV (AD169) propagated in HFFs with CMX001 for 10 months to generate a CMX001 resistant strain (CMX001\(^R\))

**CMX001\(^R\):**
- No mutations in UL97
- One mutation in CMV polymerase UL54 \(\rightarrow\) D542E
  - Recombinant >10-fold increase in EC\(_{50}\) to CDV and CMX001
  - Sensitive to GCV and FOS
  - Small plaque phenotype and slow replication

See Prichard et al. Abstract #182 for details

GCV = ganciclovir; FOS = foscarnet; HFF = human foreskin fibroblast
Source: James et al. AAC published ahead of print 6 May 2013
CMX001-201: Evidence of CMV Prevention in Phase 2

- **Patient population:**
  - 230 allogeneic hematopoietic stem cell transplant recipients
  - Recipient seropositive for CMV (R+) with or without CMV viremia prior to dosing

- **Study 201 design:**
  - Dose-escalation: 40 – 100 – 200 mg doses of CMX001 evaluated
  - Once-weekly (QW) and twice weekly (BIW) dosing schedules
  - 9-11 weeks dosing from engraftment through ~Day 100 post-HSCT

- **Primary endpoint: Failure of CMV prevention**
  - CMV disease, OR
  - CMV DNA (PCR) > 200 copies/mL at end of treatment
Twice-weekly CMX001 Dosing Decreased CMV Events

- 100 mg BIW dosing better than 200 mg QW
- QW dosing appears to provide suboptimal drug pressure
- 40 mg QW dose ineffective

Source: Data from Study 201 presented at BMT Tandem, February 2012.
# Study 201: CMX001 Suppressed CMV Reactivation

<table>
<thead>
<tr>
<th>Placebo</th>
<th>CMX001 100 mg BIW</th>
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<tbody>
<tr>
<td>• N = 47</td>
<td>• N = 41</td>
</tr>
<tr>
<td>• 15/47 ≥ 1,000 c/mL</td>
<td>• 0/41 ≥ 1,000 c/mL</td>
</tr>
<tr>
<td></td>
<td>• 9/41 CMV PCR+</td>
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*Represents clinically relevant threshold. Subjects CMV negative at Baseline.

Source: Data from Study 201 presented at BMT Tandem, February 2012.
No Resistance-Associated Mutations (RAMs) Detected in Study 201

- All patients with >200 c/mL of CMV DNA in plasma at any time on study had samples submitted for UL54 and UL97 genotyping (Viracor-IBT)

- UL97 Kinase: No RAMs detected

- UL54 Polymerase: R1052C detected in 3 subjects (at baseline in one case)
  - R1052C in combination with V781I, N885T, S897L, and A1122T previously associated with CDV resistance in a clinical isolate from a GCV/FOS treated patient (Smith 1997 JID 176:69-77)

- D542E was not detected
Recombinant Phenotyping of R1052C Demonstrated Sensitivity to Both CDV and CMX001

- Clone UL54 R1052C (+ A885T, S897L variation in clinical samples) in plasmid
- Use to mutagenize wt CMV BAC clone (AD169 strain with SEAP reporter)
- Transfect BAC into HFF cultures to recover live recombinant (mutant) CMV
- SEAP yield reduction assays to determine EC50 for wt and recombinant CMV

<table>
<thead>
<tr>
<th></th>
<th>CMX001</th>
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<th>Cidofovir</th>
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<tbody>
<tr>
<td></td>
<td>EC50 (nM)</td>
<td>SD</td>
<td>N</td>
<td>Fold Change</td>
</tr>
<tr>
<td><strong>Wild Type Control</strong></td>
<td>0.22</td>
<td>0.09</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td><strong>Recombinant [R1052C, A885T, S897L]</strong></td>
<td>0.17</td>
<td>0.07</td>
<td>8</td>
<td><strong>0.8</strong></td>
</tr>
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\(^1\text{Chou, personal communication}\)
Conclusions

- **Primary resistance profile:** resistance to first line CMX001 slow to emerge *in vitro* and in treatment-naïve patients
  - Primary CMX001 resistance *in vitro* associated with maintained sensitivity to GCV and FOS and decreased viral replication
  - No mutations associated with phenotypic resistance to CMV antivirals emerged in Study 201

- **Cross resistance profile:** UL54 mutations associated with other CMV antivirals (GCV, CDV) can cause cross resistance to CMX001 *in vitro* and diminish virologic response in CMV therapy experienced patients
  - UL54 mutations may confer resistance in previously treated patients
  - UL97 mutations do not confer resistance due to inherent phosphonate in CMX001

GCV = ganciclovir; FOS = foscarnet
CMV DNA Polymerase (UL54) Mutations/Associated Phenotypes

CMX001 Expanded Access Protocol: Study 350 (n=210)

- Part of CMX001 Expanded Access Program to treat life-threatening dsDNA viral infections in patients who had exhausted all available therapies or for whom there were no therapeutic options available

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<th>Baseline Demographics</th>
<th>dsDNA Viral Infection(s)</th>
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<tbody>
<tr>
<td><strong>N = 210</strong></td>
<td><strong>28% had two or more viral infections</strong></td>
</tr>
<tr>
<td>– 68 pediatric, 142 adult</td>
<td></td>
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<tr>
<td><strong>CMX001 Exposure</strong></td>
<td><strong>Breakdown by virus:</strong></td>
</tr>
<tr>
<td>– Mean 9.5 weeks (1-43 weeks)</td>
<td>– 107 – CMV</td>
</tr>
<tr>
<td>– 68% &gt; 4 weeks</td>
<td>– 61 – AdV</td>
</tr>
<tr>
<td>– 30% &gt; 12 weeks</td>
<td>– 7 – BKV</td>
</tr>
<tr>
<td><strong>Immunodeficiency</strong></td>
<td>– 35 – Other</td>
</tr>
<tr>
<td>– 153 HSCT (73%)</td>
<td><strong>Genotyping for CMV UL54 and UL97 attempted for all patients with &gt;500 c/mL</strong></td>
</tr>
<tr>
<td>– 33 SOT (16%)</td>
<td><strong>Majority of UL54 mutations observed confer GCV/CDV resistance</strong></td>
</tr>
<tr>
<td>– Congenital, HIV, other (11%)</td>
<td></td>
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</table>

GCV = ganciclovir; FOS = foscarnet
Plasma CMV Response for Patients in Study 350 by Baseline CMV Genotype at Last Time on Therapy

- % with ≥0.5 log10 response or maximum response
- % ≤200c/mL

Wildtype (n=53) | UL97 (n=24) | UL54 (n=4)
--- | --- | ---

Percent of Patients Responding

0 10 20 30 40 50 60 70
# UL54 Mutations Associated with Diminished Response CMV Therapy (GCV, FOS, CDV) Experienced Population

<table>
<thead>
<tr>
<th></th>
<th>UL54 Mutation[1] (n=14)</th>
<th>No UL54 Mutation (n=49)</th>
<th>No GT Obtainable (n=7)</th>
</tr>
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<tbody>
<tr>
<td>Mean Baseline Viral Load (c/mL)</td>
<td>10,965</td>
<td>5,495</td>
<td>457</td>
</tr>
<tr>
<td>Mean log₁₀ Change (Baseline to Week 5)</td>
<td>-0.77</td>
<td>-0.64</td>
<td>-0.51</td>
</tr>
<tr>
<td>Proportion ≤200 c/mL at Week 5</td>
<td>0/14 (0%)</td>
<td>15/49 (31%)*[2]</td>
<td>6/7 (86%)</td>
</tr>
<tr>
<td>Mean log₁₀ Change (Baseline to Last Value)</td>
<td>-0.43</td>
<td>-0.81</td>
<td>-0.67</td>
</tr>
<tr>
<td>Proportion ≤200 c/mL at Last Value</td>
<td>0/14 (0%)</td>
<td>26/49 (53%)*[2]</td>
<td>7/7 (100%)</td>
</tr>
</tbody>
</table>


[2] p-value <0.05 using Fisher’s exact test (two-sided) vs. UL54 mutation group
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# Acknowledgements

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