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CMX001 is a Potential Treatment for Adenovirus Infection: Preliminary Antiviral Activity Results from an Open-label, Expanded Access Study of CMX001 for the Treatment of Serious or Life-threatening Diseases Caused by Double-stranded DNA Viruses

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- Michael Grimley - None

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Adenovirus

- Adenovirus (AdV) is a serious and often fatal infection in immunocompromised patients
- AdV infections in hematopoietic cell transplant (HCT) recipients are more severe, often disseminated and, once established, often rapidly fatal even with treatment
- Estimates of the incidence of AdV infections in HCT recipients range from 5-47% with reported mortality rates ranging from 11-50%

Ljungman P, Eur J Clin Microbiol Infect Disease 2004
Nihal G et al, BBMT 2012

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Adenovirus

- Incidence of AdV infections in HCT recipients is increasing, likely secondary to increased use of T cell depleted allografts and cord blood as a donor source
- Patients with GVHD have increased rates of AdV infection
- No antiviral drugs are currently approved for treatment of AdV infections though IV Cidofovir (CDV) has been used with variable efficacy, however its use is associated with a high incidence of nephrotoxicity
- A virologic response to treatment with IV CDV has been associated with clinical improvement
- Failure to achieve a >1log10 decrease in viral load (VL) during the first two weeks of therapy is associated with poorer patient outcomes

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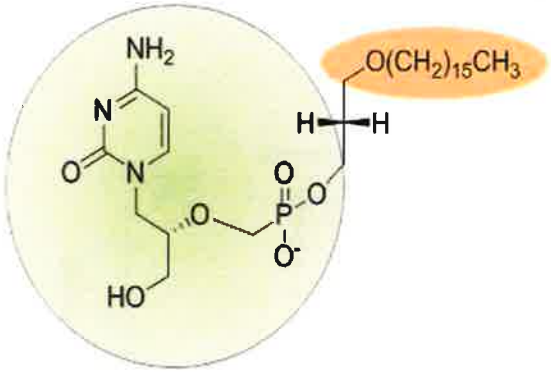
CMX001



Karl Hostetler, MD

- Orally available lipid-conjugate of the nucleotide analog cidofovir (CDV)
- High intracellular antiviral concentration
  - 700-fold more CDV-PP than CDV in PBMCs
- Orally bioavailable with a long half-life
  - Intracellular CDV-PP $t_{1/2}$ = 6.5 days
- Broad spectrum activity against dsDNA viruses
  - 19 to >4,000-fold more potent than CDV against AdV, herpes, papilloma, polyoma, and pox viruses *in vitro*
- 65-fold more potent against AdV than CDV *in vitro*
  - EC_{50} < 0.02 uM against AdV
- Enrollment complete in Phase 2 AdV study; data expected 2H 2013*
- Initiating Phase 3 for the prevention of CMV in HCT recipients*

Beadle at al AAC 2002: 46:2381-6

* ClinicalTrials.gov: NCT01241344

* ClinicalTrials.gov: NCT01769170

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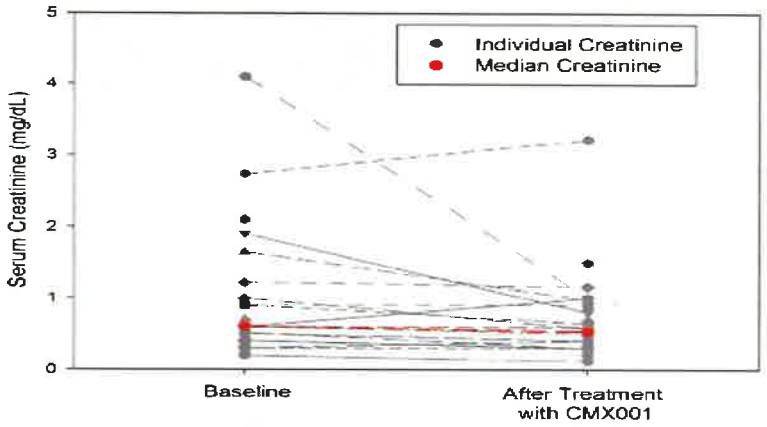
CMX001 –Lack of Nephrotoxicity

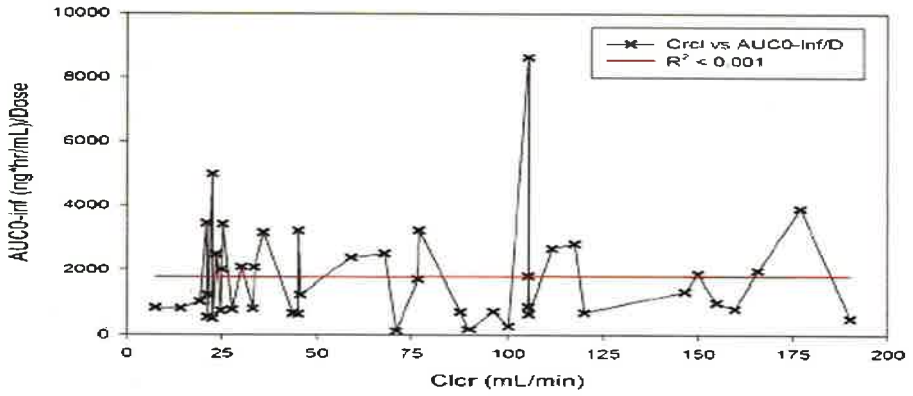
CMX001

CMX001 has shown no evidence of nephrotoxicity in clinical and nonclinical studies conducted to date.*

Renal function improved or remained unchanged in the majority of EIND patients during administration of CMX001



Renal impairment does not alter systemic exposure (AUC) to CMX001 compared to patients with normal renal function.



* Data reported at ICAAC, Boston, MA 2010

CMX001 is not a substrate of human organic anion transporter 1

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CMX001 Expanded Access Program

- CMX001 access for patients with life-threatening dsDNA viral infections and no therapeutic options

- Emergency INDs (EINDs) (n =228 as of February 2013)
  - 100+ centers in US, Canada, France, UK, Austria, Switzerland, Spain, Israel and Chile
  - >230 adult and pediatric patients with CMV, AdV, BKV, HSV, JCV, HHV, VZV or HPV
  - March 2009 – March 2012 (with limited exceptions since)

- Expanded Access Protocol: Study 350* (n=210)
  - 36 sites in US from November 2010 – March 2012
  - November 2010 – July 2011: all dsDNA viruses included
  - July 2011 – March 2012: Protocol limited to CMV, HSV or AdV

*CMX001-350: ClinicalTrials.gov: NCT01143181

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CMX001-350

- Eligibility: Immediate life-threatening or serious disease or condition caused by infection by a dsDNA virus

- Duration of Treatment: In patients who demonstrate a clinical and virologic response to treatment with CMX001, treatment was continued until virology assessments of any previously positive culture or PCR sites yield negative tests for 4 successive weeks. In patients at high risk of recurrence of viral infection, treatment may be continued for up to a total of 6 months

- Study Completion was 30 days after last CMX001 dose

*CMX001-350: ClinicalTrials.gov: NCT01143181

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CMX001-350: Dosing and Study Procedures

- CMX001 dose
  - 100 mg BIW for adults/adolescents
  - 2 mg/kg/dose BIW for pediatric patients (< 12 years of age and < 40 kg)
  - Dosing changed due to GI side effects in 2011: Prior dosing
    - 200 mg BIW for Adults
    - 4 mg/kg/dose BIW for pediatric patients
- AdV Viral Load Measurements
  - Baseline (BL)
  - During Treatment (weekly)
  - 1 and 4 weeks post treatment

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Demographics

- 57 patients
  - 27 pediatric patients
    - Ages 4 months – 12 years
    - 11 female, 16 male
  - 30 adult patients
    - Ages 15-68 years
    - 11 female, 19 male

- Immunodeficiency
  - 47(83%) HSCT
  - 7 (12%) Solid Organ Transplant
  - 3 (5%) Other

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Viral Burden

- 33 (58%) Infected with AdV only
- 24 (42%) Co-infected with other dsDNA viruses

- 16 (28%) Disseminated
  - 6 Unspecified, 1 Encephalitis/Lung, 2 GI/Bladder, 1 GI/Lung, 3 Lung/Kidney or Bladder, 1 Peritoneal Fluid/GI/Lung, 1 Peritoneal/Bladder, 1 Kidney/GI
  - 13/16 with Viremia
- 26 (46%) Localized
  - 7 Bladder, 9 GI, 4 Liver, 5 Lung, 1 Kidney
  - 19/26 with Viremia
    - 4 GI, 2 Bladder, 1 Lung w/o viremia
- 15 (26%) Viremia Only

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Anti-Viral Therapy

- 25 (44%) of patients had prior IV CDV therapy
  - Mean (SD): 16 (23) days
  - Median (IQR, Range): 9 (1-22, 1-112) days

- CMX001 Exposure
  - Mean 9 weeks (1-43 weeks)
  - 67% > 4 weeks
  - 33% > 12 weeks

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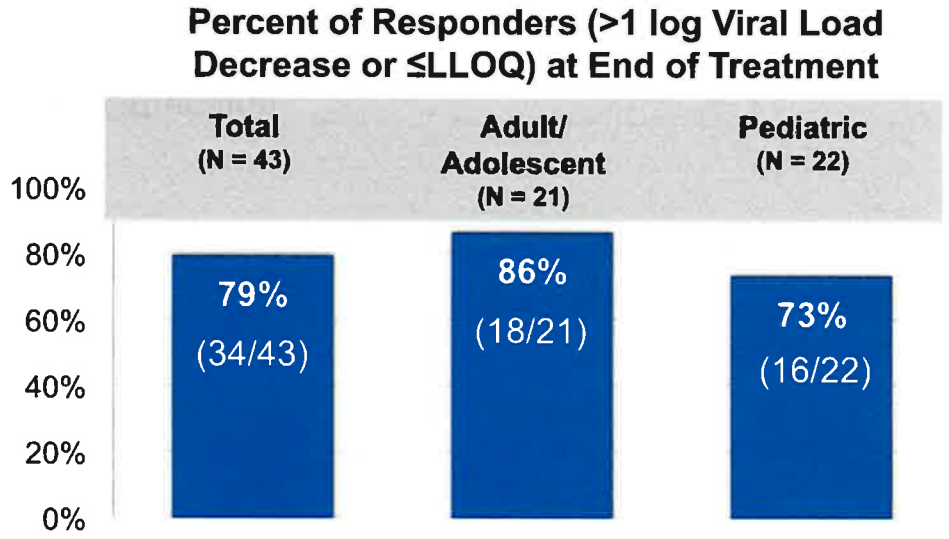
Response to CMX001 Treatment



Percent of Patients with AdV Viremia ≤ LLOQ	**51% (22/43)**	**48% (10/21)**	**55% (12/22)**
Median Viral Load Drop (log10 copies/mL)	1.6	2.2	1.2

End of treatment was defined as last viral load sample up to 7 days following last dose of CMX001, or last viral load sample if last dose of CMX001 is unknown. Patients were excluded due to viral load at baseline ≤ 100 copies/mL (LLOQ).

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Outcomes

- 30/57 (53%) patients were alive at study completion

	Disseminated (n=16)	Localized (n=26)	Viremia (n=15)	Total (n=57)
Alive	4	16	10	30
Dead	12	10	5	27
AdV	6	3	0	9
Relapse	0	2	1	3
Other*	6	5	4	15

* Bacterial, Fungal, GVHD, AE, Other viral

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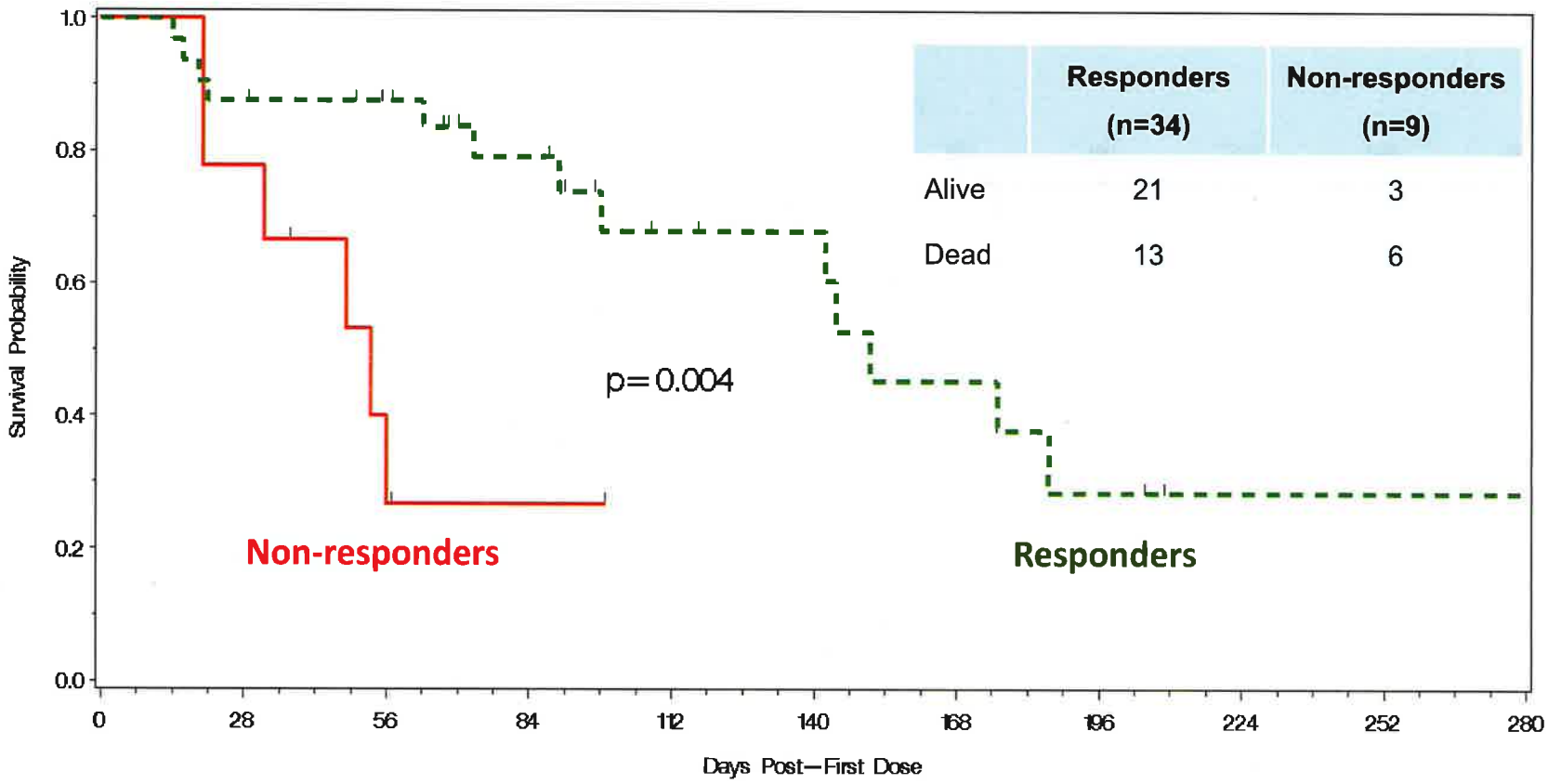
All-Cause Mortality at Study Completion by AdV Viral Response



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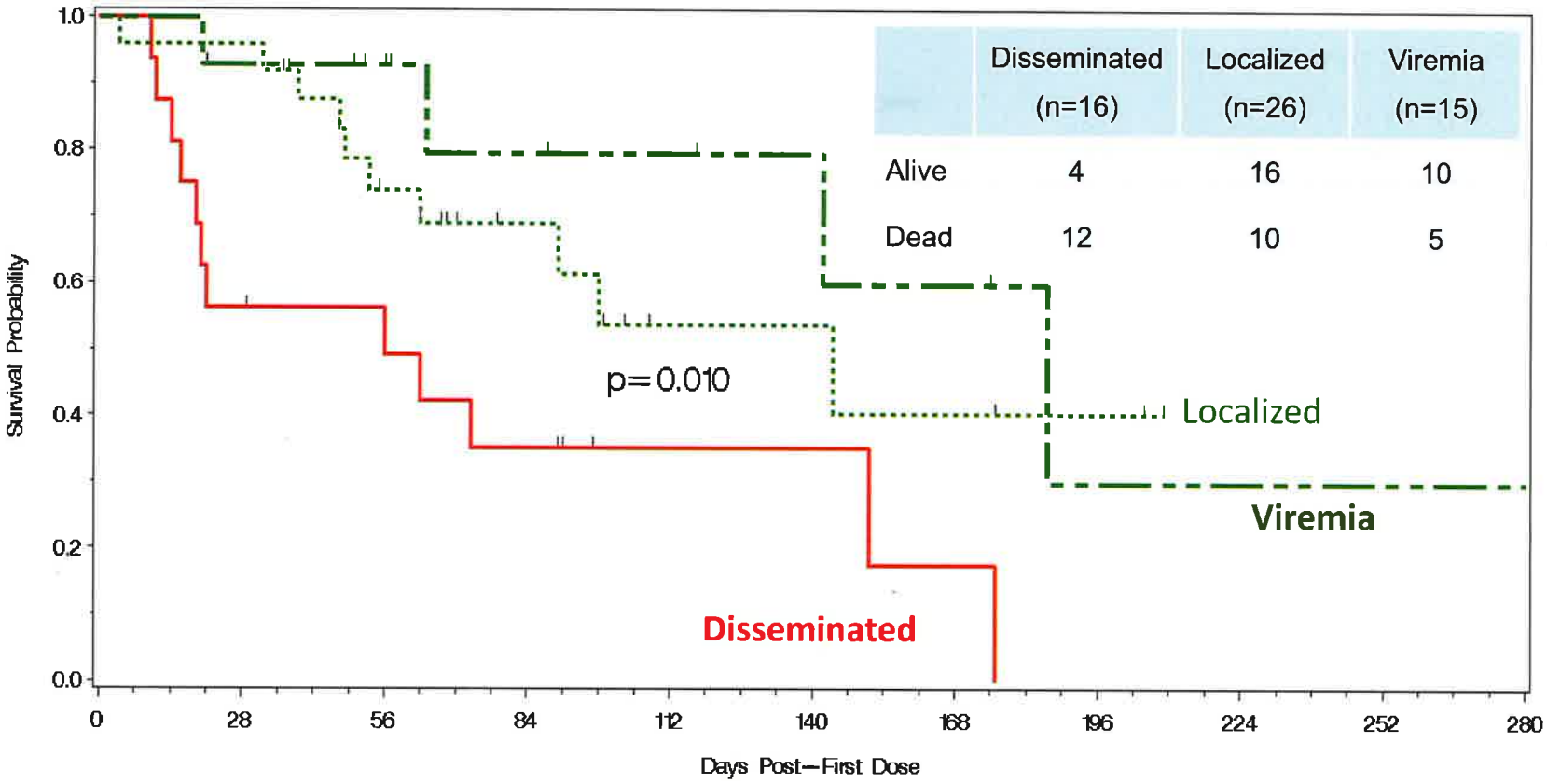
All-Cause Mortality at Study Completion in ADV Subjects by Extent of Disease



	Disseminated (n=16)	Localized (n=26)	Viremia (n=15)
Alive	4	16	10
Dead	12	10	5

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Conclusions

- Majority of the patients had a virologic response
- Favorable safety profile was observed with no evidence of nephrotoxicity
- Patients who had a virologic response had better outcomes
- Patients with a lower disease burden had better outcomes
- Role of CMX001 as preemptive therapy for AdV is under investigation (Phase 2 AdV Study-completed March 2013)
- CMX001 is a promising therapeutic option for the treatment of AdV infections

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