

IDWeek 2014, Session: 186, Late Breaker Oral Abstracts  
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# **Preliminary Safety Results and Antiviral Activity from the Open-label Pilot Portion of a Phase 3 Study to Evaluate Brincidofovir for the Treatment of Adenovirus Infection**

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# Disclosure Statement : Jo-Anne Young, MD

Clinical investigator for/research support from:

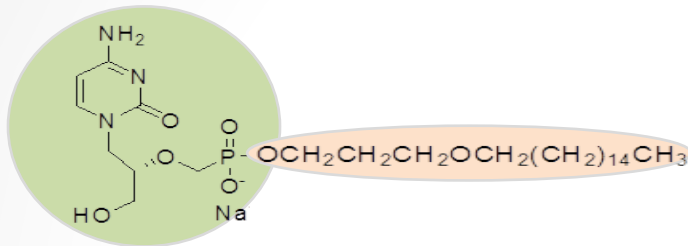
- Chimerix, Inc.
- GlaxoSmithKline plc
- Merck & Co., Inc.
- ViroPharma, Inc.

# Adenovirus: High Unmet Medical Need

- Adenovirus (AdV) causes a wide spectrum of disease ranging from asymptomatic viremia to severe, disseminated disease, particularly in recipients of allogeneic hematopoietic cell transplants (HCT)
- Reported incidence of AdV infection in allo HCT is 5 to 47%<sup>1</sup>
- Untreated, mortality rates of up to 26% are reported for HCT patients with symptomatic infection<sup>2</sup> and 60 to 80% for disseminated disease<sup>1-4</sup>
- Risk factors include young age, receipt of T cell-depleted graft, mismatched or unrelated graft, or cord blood, and presence of acute GvHD<sup>5</sup>
- Current treatment strategies typically involve supportive care with a reduction in immune suppression and/or initiation of antiviral treatment, typically IV CDV despite the risk of significant renal injury

# Brincidofovir (CMX001, BCV)

- BCV is a lipid-conjugate of CDV which allows for oral dosing and high intracellular uptake, delivering high intracellular levels of the active antiviral

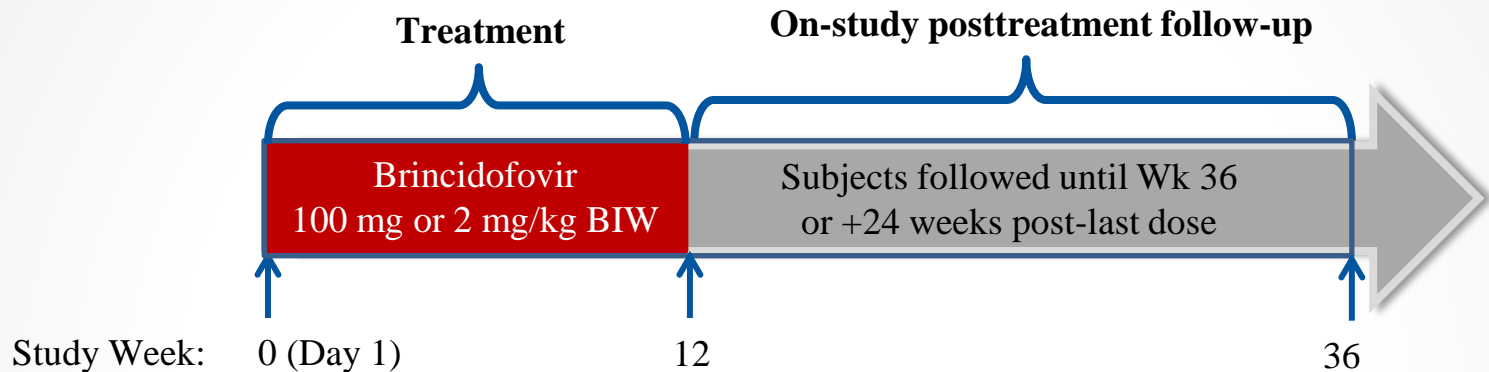


- Broad spectrum *in vitro* activity against dsDNA viruses
- No evidence of nephrotoxicity; unlike IV CDV, BCV is not concentrated in renal tubules by organic anion transporter 1 (hOAT-1)
- No observed hematologic toxicity, including early after HCT
- Anti-AdV activity confirmed when BCV used as preemptive therapy for allo HCT patients with asymptomatic AdV viremia in Phase 2 (CMX001-202; NCT01241344)
- In expanded-access study (CMX001-350; NCT01143181):
  - Patients with AdV disease showed improved survival compared to historical data
  - All-cause mortality was lower when BCV was initiated for AdV viremia vs. disseminated AdV disease

# CMX001-304: Study Overview

- Study CMX001-304 (NCT02087306) is being conducted in two parts: first part (“pilot”) in up to 100 patients was initiated to guide final design
- In pilot part, subjects assigned to one of three cohorts:
  - **Cohort A:** allo HCT recipient at risk of AdV disease progression (i.e., asymptomatic viremia  $\geq 1000$  c/mL or localized disease in one organ system and plasma viremia  $< 1000$  c/mL)
  - **Cohort B:** allo HCT recipient with disseminated AdV disease (symptomatic disease in two organ systems, or one organ system with plasma viremia  $\geq 1000$  c/mL), or
  - **Cohort C:** all other patients (inc. auto HCT, SOT, primary immune deficiency, HIV, chemotherapy, etc.) regardless of disease status

# CMX001-304: Study Design



- Open label BCV treatment for all cohorts:
  - Adults and children  $\geq 50$  kg: BCV 100 mg twice a week
  - Children 2 months or older and  $< 50$  kg: BCV 2 mg/kg twice a week
- AdV viral load values in plasma and other body fluids measured by central virology laboratory using the 7500 Adenovirus Quantitative Real-time PCR Test (lower limit of detection = 100 c/mL; lower limit of quantification = 190 c/mL)

## CMX001-304: Enrollment

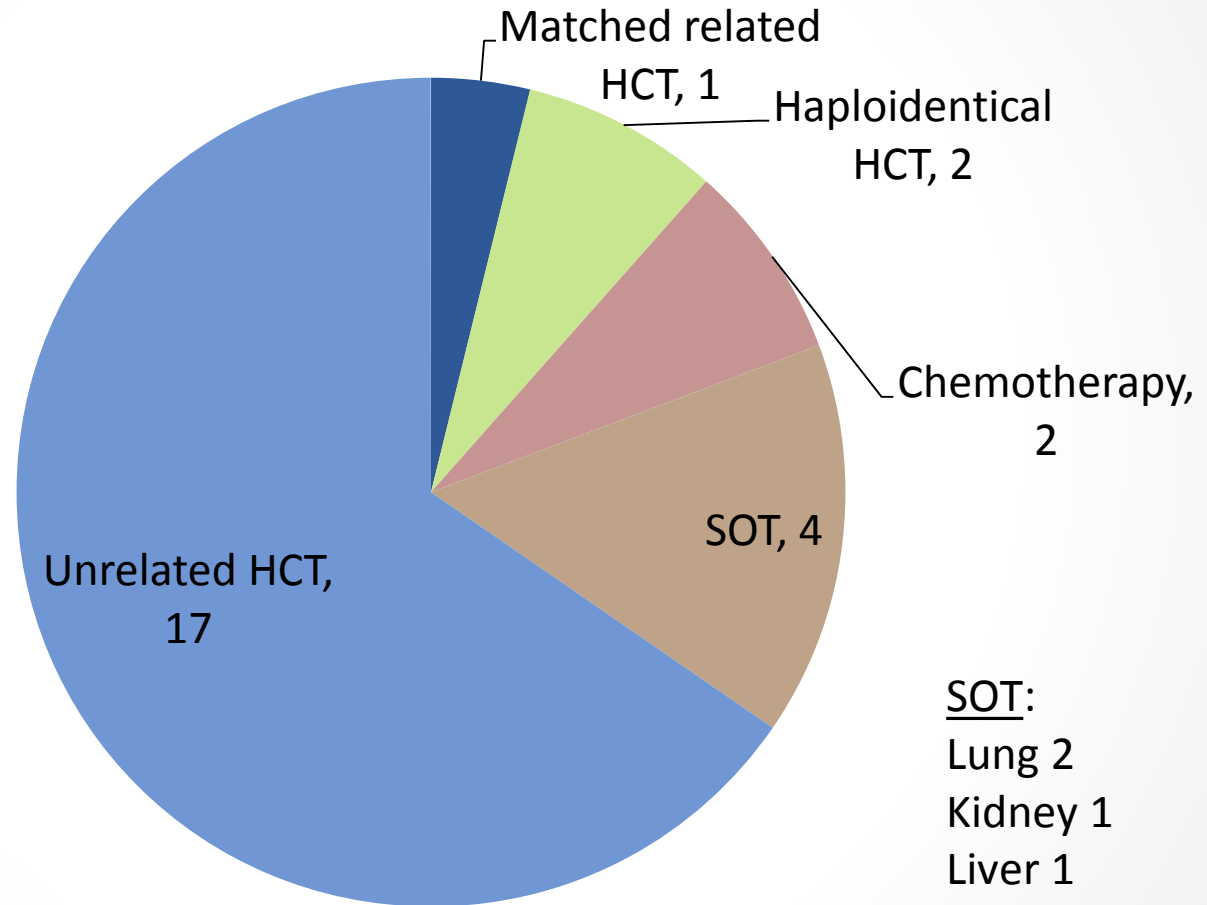
- As of 19-Sep-2014, a total of 48 subjects across 17 centers have enrolled in pilot portion
  - Protocol generally initiated at each site for a symptomatic patient, resulting in delay from identification to first dose for first patient (typically 2 weeks or more)
  - Data include preliminary safety and antiviral activity data from first 26 subjects enrolled through 15-Jul-2014.
    - These subjects have had opportunity for ~2 months of observation

## Subject Demographics (N = 26)

<b>Age Category [n (%)]</b>	< 2 yrs	6 (23%)
	2 to 5 yrs	6 (23%)
	6 to 11 yrs	3 (12%)
	12 to 17 yrs	5 (19%)
	<b>≥ 18 years</b>	<b>6 (23%)</b>
<b>Sex [n (%)]</b>	Female	9 (35%)
	<b>Male</b>	<b>17 (65%)</b>
<b>Race [n (%)]</b>	Asian	1 (4%)
	Black	5 (19%)
	Other	3 (12%)
	<b>White</b>	<b>17 (65%)</b>
<b>Treatment Cohort [n (%)]</b>	A (Allo HCT, asymptomatic viremia or localized disease)	4 (15%)
	<b>B (Allo HCT, disseminated disease)</b>	<b>16 (62%)</b>
	C (Other than allo HCT with or w/out disease)	6 (23%)



# Patient Subgroups



## Viral Characteristics (N = 26)

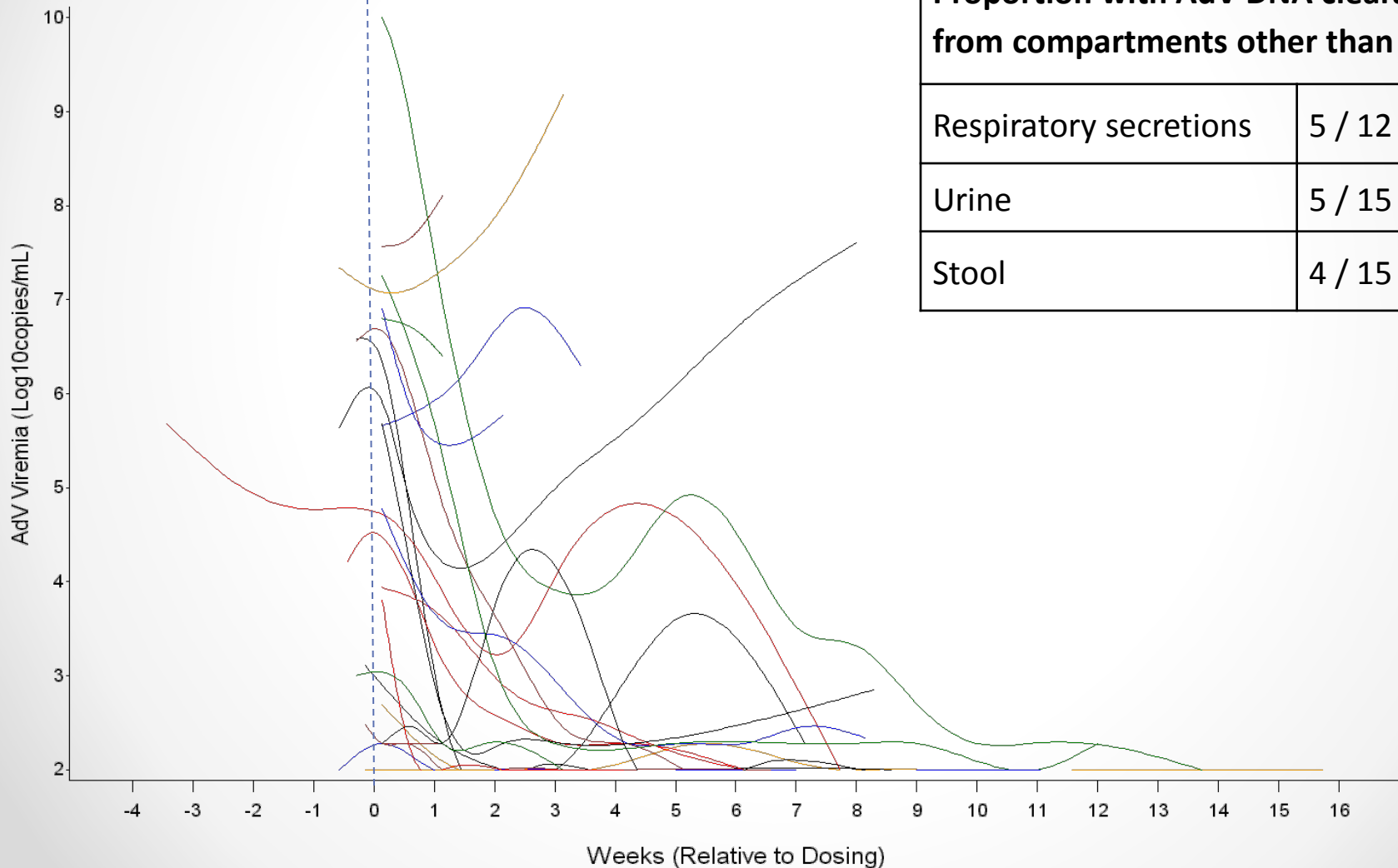
AdV Plasma DNA Viral Load [n (%)]	Not detected	1 (4%)
	< LLOQ, detected	4 (15%)
	< 10 <sup>3</sup> c/mL	1 (4%)
	10 <sup>3</sup> to < 10 <sup>4</sup> c/mL	4 (15%)
	<b>≥ 10<sup>4</sup> c/mL</b>	<b>14 (54%)</b>
	Unknown	2 (8%)
AdV Positivity by Site [n (%)]	Urine	15 (58%)
	Stool	15 (58%)
	Respiratory secretions	12 (46%)
AdV Signs and Symptoms [n (%)]	Pneumonitis	11 (42%)
	Hepatitis	4 (15%)
	Enterocolitis	6 (23%)
	Nephritis	7 (27%)
<b>Prior Treatment with IV CDV [n (%)]</b>	Yes	<b>11 (42%)</b>

- Other dsDNA viruses: **27% BKV** in urine; **19% CMV** in plasma, and **8% EBV** in plasma detected by PCR at baseline
- AdV serotypes: plasma AdV typed for 18 subjects and included species A31 (n=3), B[11,34,35] (n=4), C[1,2,5,6] (n=10) and one subject with a mix of B11 and C5/6

# Subject Disposition / Treatment Duration

- Of first 26 subjects enrolled, as of 12 Sep 2014:
  - 4 subjects have completed treatment
  - 13 subjects discontinued treatment prematurely:
    - death = 4 (15%);
    - AE = 3 (12%);
    - physician decision = 2 (8%);
    - start other AdV therapy = 2 (8%);
    - progression of transplant qualifying disease = 1 (4%)
    - withdrew consent = 1 (4%)
  - In 9 subjects, treatment is ongoing
- Median BCV treatment duration:  
**54 days** (range 1- 108)

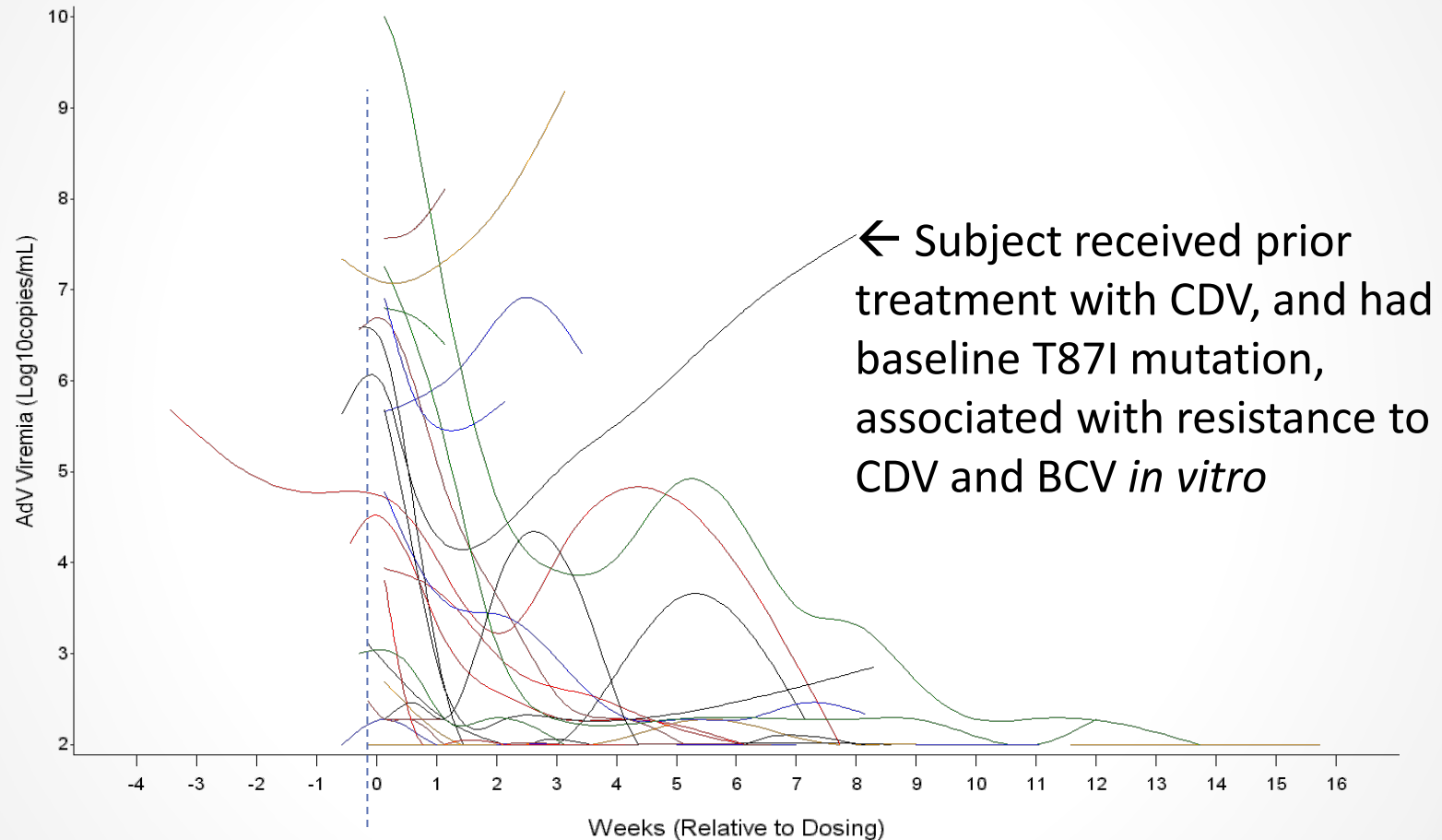
# Change in Plasma AdV DNA over Time: All Subjects



**Proportion with AdV DNA clearance  
from compartments other than plasma**

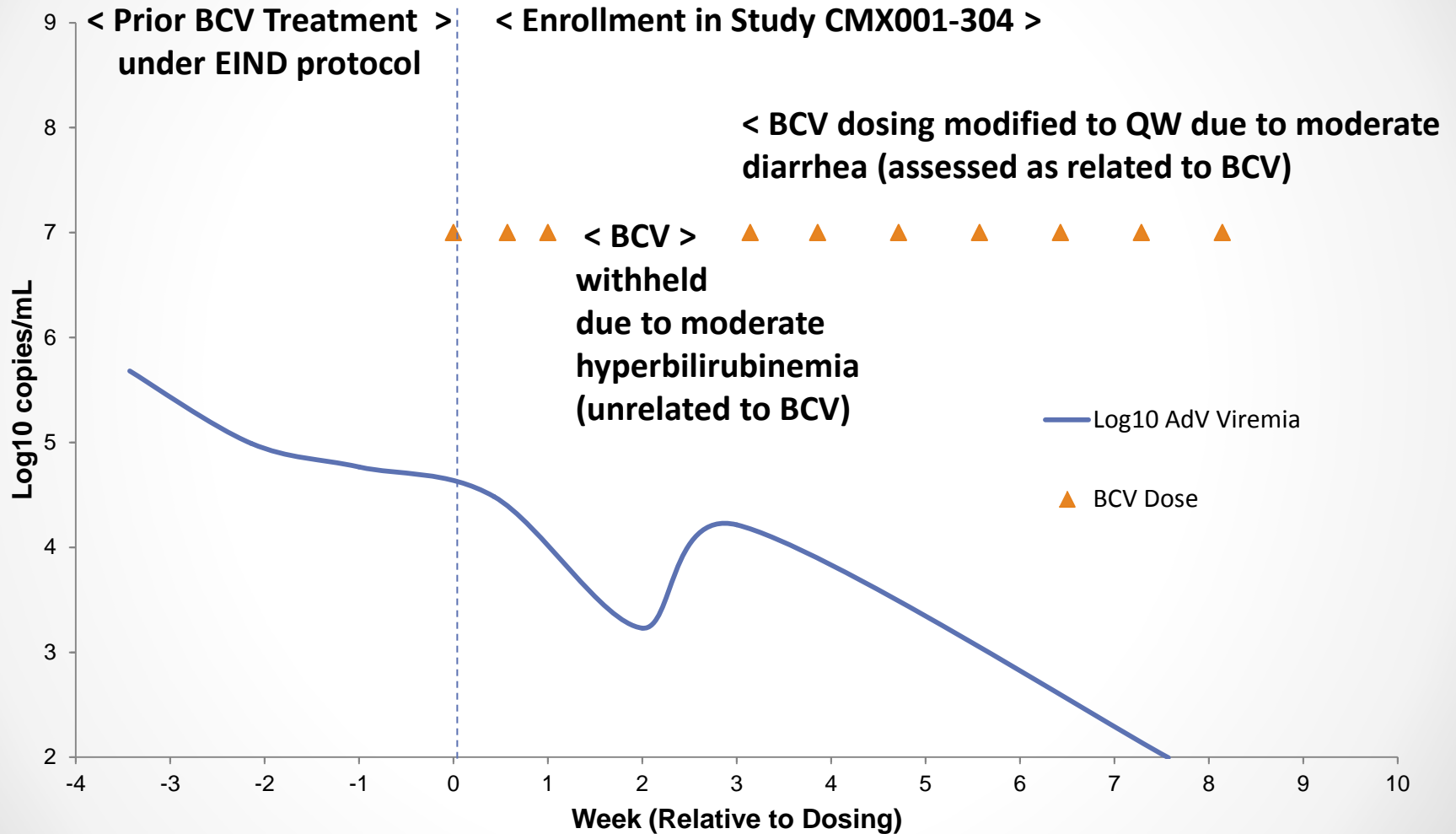
Respiratory secretions	5 / 12 (42%)
Urine	5 / 15 (33%)
Stool	4 / 15 (27%)

# Change in Plasma AdV DNA over Time: All Subjects



**Prior CDV use may be associated with non-response, yet of the 11 patients with prior IV CDV, 6 reached undetectable levels and one had  $> 2\log_{10}$  decline at last on-treatment.**

# Treatment Interruption



# Strong Virologic Responses Observed with BCV

**15/23 (65%) had  $\geq 3 \log_{10}$  reduction or undetectable levels at nadir**

**Median (range) change from baseline to nadir in plasma AdV DNA:  
-1.44  $\log_{10}$  c/mL (- 8.00 to - 0.62  $\log_{10}$ )**

	Baseline AdV Plasma Viremia ( $\log_{10}$ c/mL)	Cohort A (n = 3)	Cohort B (n = 16)	Cohort C (n = 4)	All Subjects (N = 23)
Undetectable plasma AdV DNA at Any Time On-Treatment	All	2/3 (67%)	10/16 (63%)	2/4 (50%)	14/23 (61%)
	< 4.0 $\log_{10}$ c/mL	1/1 (100%)	6/7 (86%)	1/1 (100%)	8/9 (89%)
	$\geq 4.0 \log_{10}$ c/mL	1/2 (50%)	4/9 (44%)	1/3 (33%)	6/14 (43%)
Undetectable plasma AdV DNA at Last On-treatment Assessment	All	2/3 (67%)	8/16 (50%)	2/4 (50%)	12/23 (54.2%)
	< 4.0 $\log_{10}$ c/mL	1/1 (100%)	5/7 (71%)	1/1 (100%)	7/9 (78%)
	$\geq 4.0 \log_{10}$ c/mL	1/2 (50%)	3/9 (33%)	1/3 (33%)	5/14 (36%)

- Similar proportion of patients with undetectable AdV viremia at the last timepoint on-treatment across all AdV subtypes (45-60%)

# Survival Improved in BCV-treated vs. Previous Reports

## CMX001-350

AdV : 31/61 (**mortality 51%**)

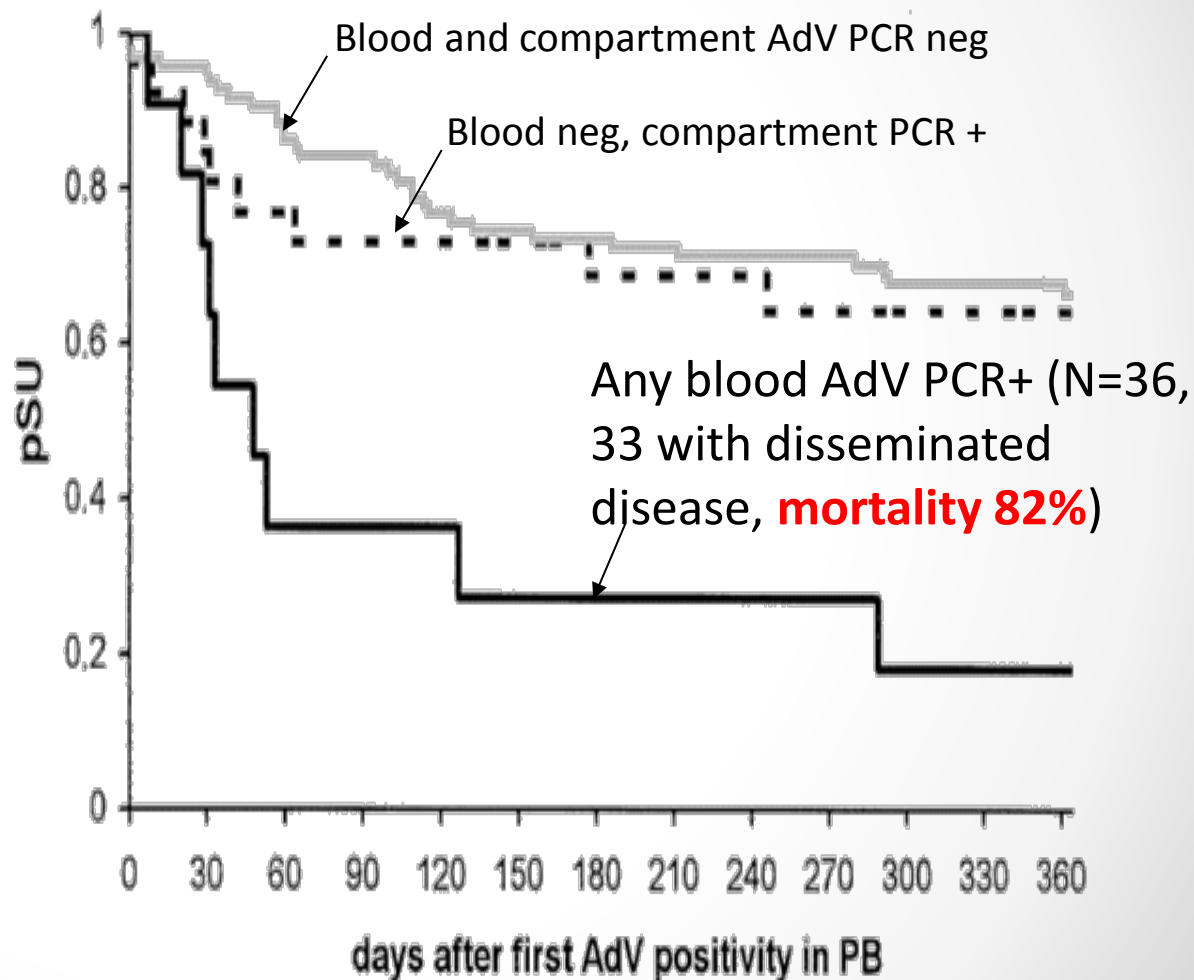
## CMX001-304

Cohorts A/B/C enrolled through 15Jul2014: 12/26 (**mortality 46%**)

All of Cohort B: Plasma AdV PCR >1000 or 2 or more compartments PCR+, 11/29 (**mortality 38%**)

All of Cohorts A/B/C: 17/48 (**mortality 35%**)

## Prospective, single center pediatric cohort (N=132)<sup>1</sup>



<sup>1</sup> Lion T, et al. Blood 2003;102(3):1114-20



# Survival Improved after BCV Treatment

- Observed mortality in CMX001-304 lower than those with disseminated AdV infection from literature and from study CMX001-350 (BCV expanded access)
  - Historic rate with SoC: 60-80%<sup>1-4</sup>
  - CMX001-350 all-cause mortality through end of study in subjects with AdV infection was 51% (31 of 61)
    - **May reflect delayed initiation of therapy and/or**
    - **impact of prior IV CDV**

<sup>1</sup> Sandkovsky U, et al. Curr Infect Dis Rep 2014;16:416-24; <sup>2</sup>Ison MG, et al. CID 2006;43:331-9; <sup>3</sup>Lion T, et al. Blood 2003;102(3):1114-20; <sup>4</sup>Williams KM, et al. J Pediatr Hematol Oncol 2009;31(11):825-31

## Summary of Safety: Adverse Events

	<b>Pediatrics (n = 20)</b>	<b>Adults (n = 6)</b>	<b>All (N = 26)</b>
Subjects with $\geq 1$ SAE	14 (70%)	6 (100%)	20 (77%)
Subjects with $\geq 1$ fatal AE*	6 (30%)	1 (17%)	7 (27%)
Subjects with $\geq 1$ <b>AE requiring treatment discontinuation</b> <sup>#</sup>	2 (10%)	1 (17%)	<b>3 (12%)</b>

\* Respiratory failure (4); AdV infection (2); AdV pneumonia, Klebsiella sepsis, multi-organ failure, septic shock, transplant failure (1 each); **none BCV related**

<sup>#</sup> Severe diarrhea in 2 subjects (both assessed as related to BCV); moderate increases in serum ALT, AST, and total bilirubin in one subject (all assessed as unrelated to BCV).

# Conclusions

- BCV demonstrated **potent virologic activity** in patients with AdV disease
  - 15 / 23 (65%) had  $\geq 3 \log_{10}$  decline in AdV DNA by PCR (or were undetectable)
- Subjects treated with BCV appeared to have **improved survival** vs. historic controls
  - Among allogeneic HCT subjects with disseminated disease, mortality was 38% (vs.  $\sim 60-80\%$  reported in literature)
- **No new safety signals** were identified in this highly complicated patient population
- Data from the pilot portion of CMX001-304 clearly **support progression** to pivotal Phase 3 study of BCV for AdV