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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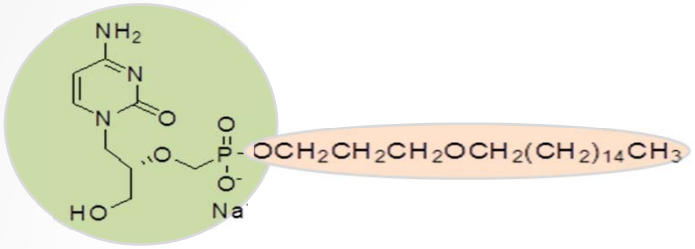
Adenovirus: High Unmet Medical Need

- 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%[1]
- Untreated, mortality rates of up to 26% are reported for HCT patients with symptomatic infection[2] and 60 to 80% for disseminated disease[1-4]
- Risk factors include young age, receipt of T cell-depleted graft, mismatched or unrelated graft, or cord blood, and presence of acute GvHD[5]
- 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

[1]Sandkovsky U, et al. Curr Infect Dis Rep 2014:16:416-24; [2]Ison MG, et al. CID 2006:43:331-9; [3]Lion T, et al. Blood 2003;102(3):1114-20; [4]Williams KW, et al. J Pediatr Hematol Oncol 2009:31(11):825-31; [5]Lungman P. Eur J Clin Microbiol Infect Dis 2004:23:583-8

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



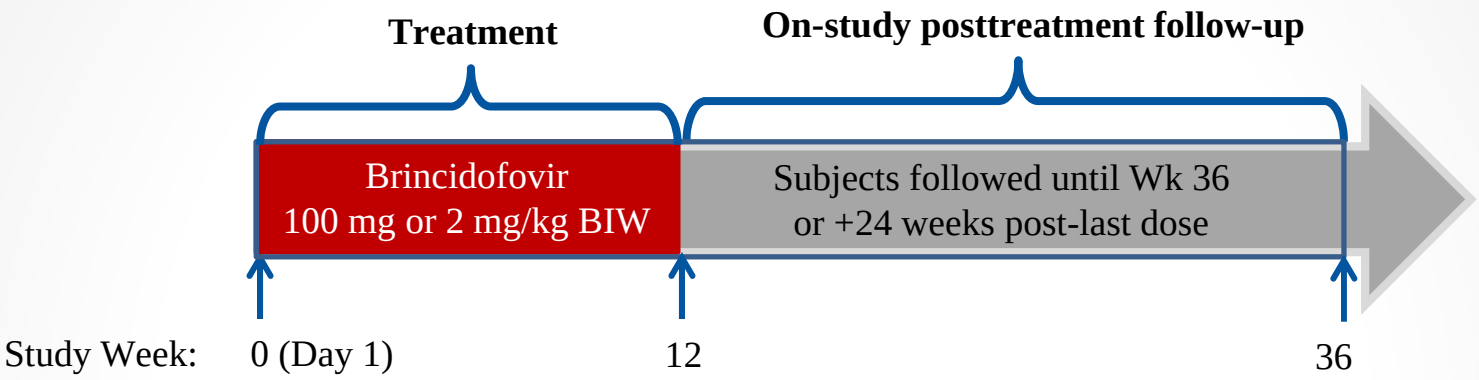
- Broad spectrum *in vitro* activity against dsDNA viruses
- No evidence of nephrotoxicity; unlike IV CDV, BCV is not concentrated in renal tubules by organic anion transporter 1 (hOAT-1)
- No observed hematologic toxicity, including early after HCT
- Anti-AdV activity confirmed when BCV used as preemptive 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 ≥ 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 ≥ 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 ≥ 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)

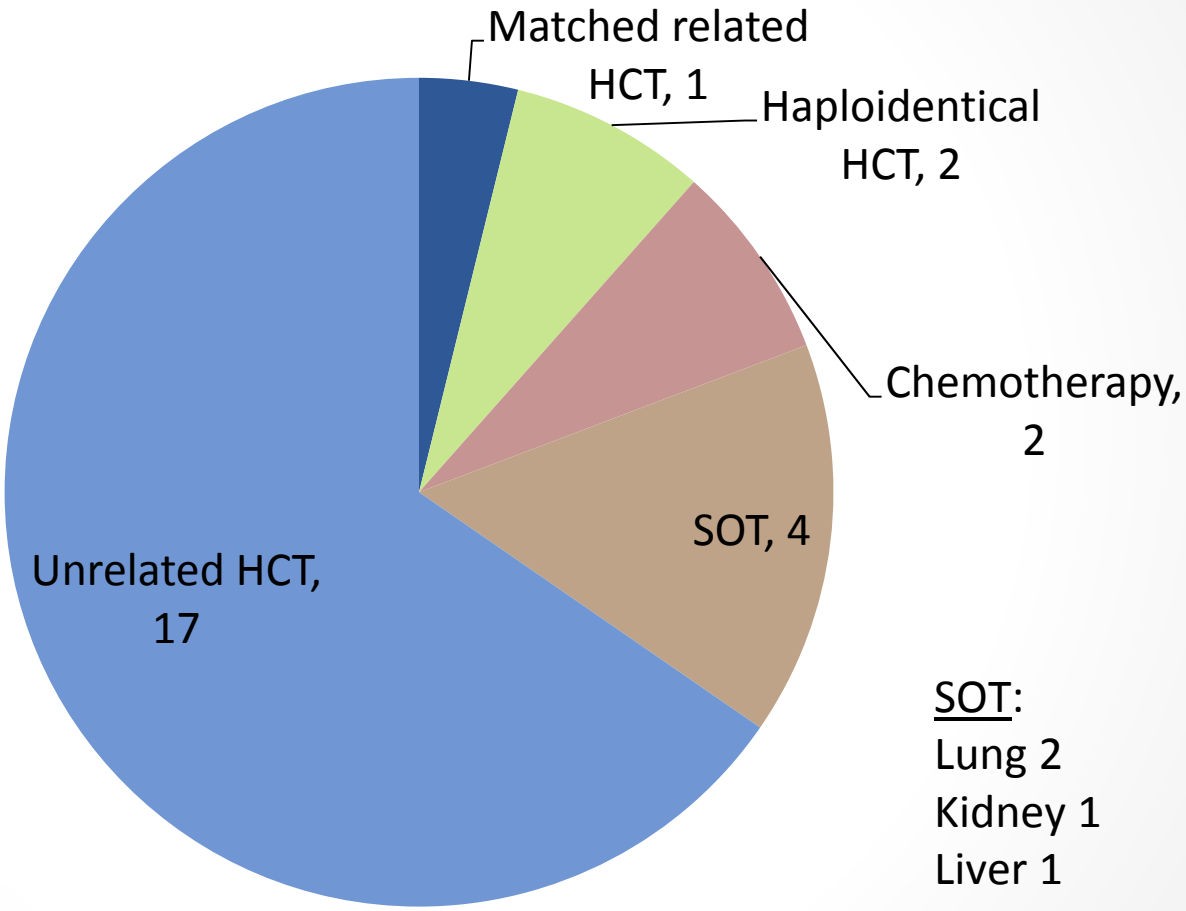
CMX001-304: Enrollment

- 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)

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

Patient Subgroups



Unrelated HCT:
MUD 8
Cord 6
Mismatched 3

SOT:
Lung 2
Kidney 1
Liver 1

Viral Characteristics (N = 26)

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

- 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

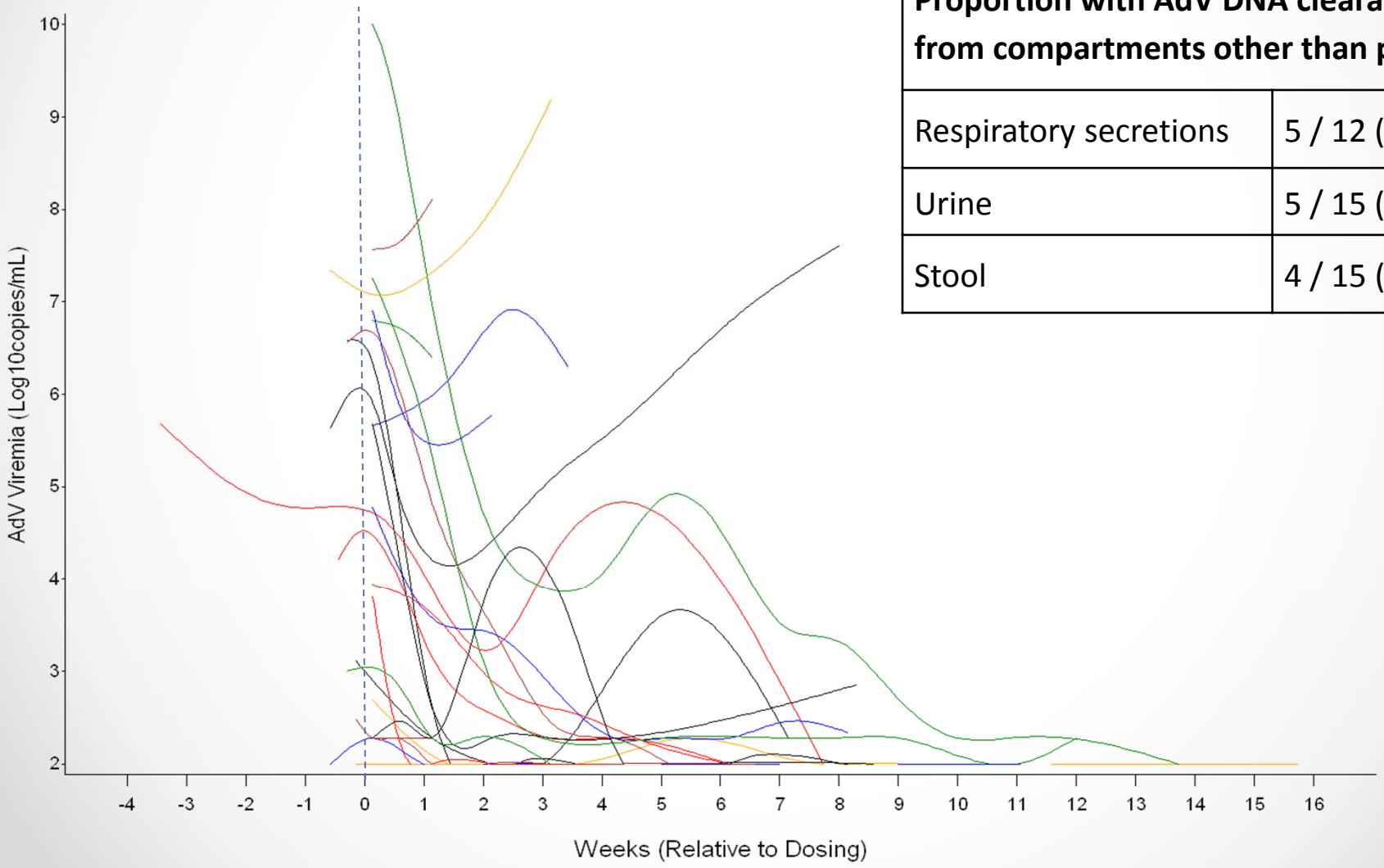
Subject Disposition / Treatment Duration

- 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:

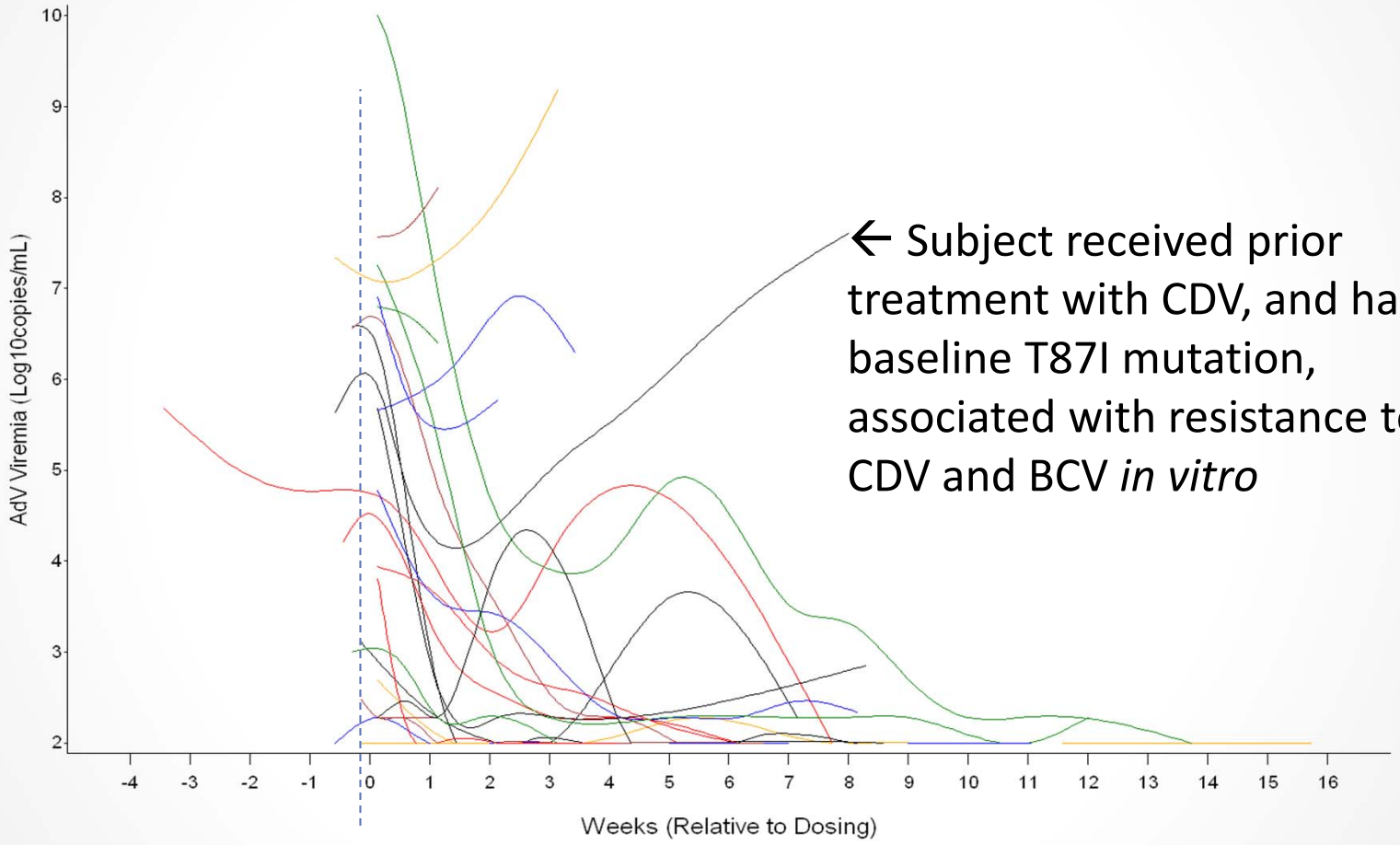
  54 days (range 1- 108)

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%)

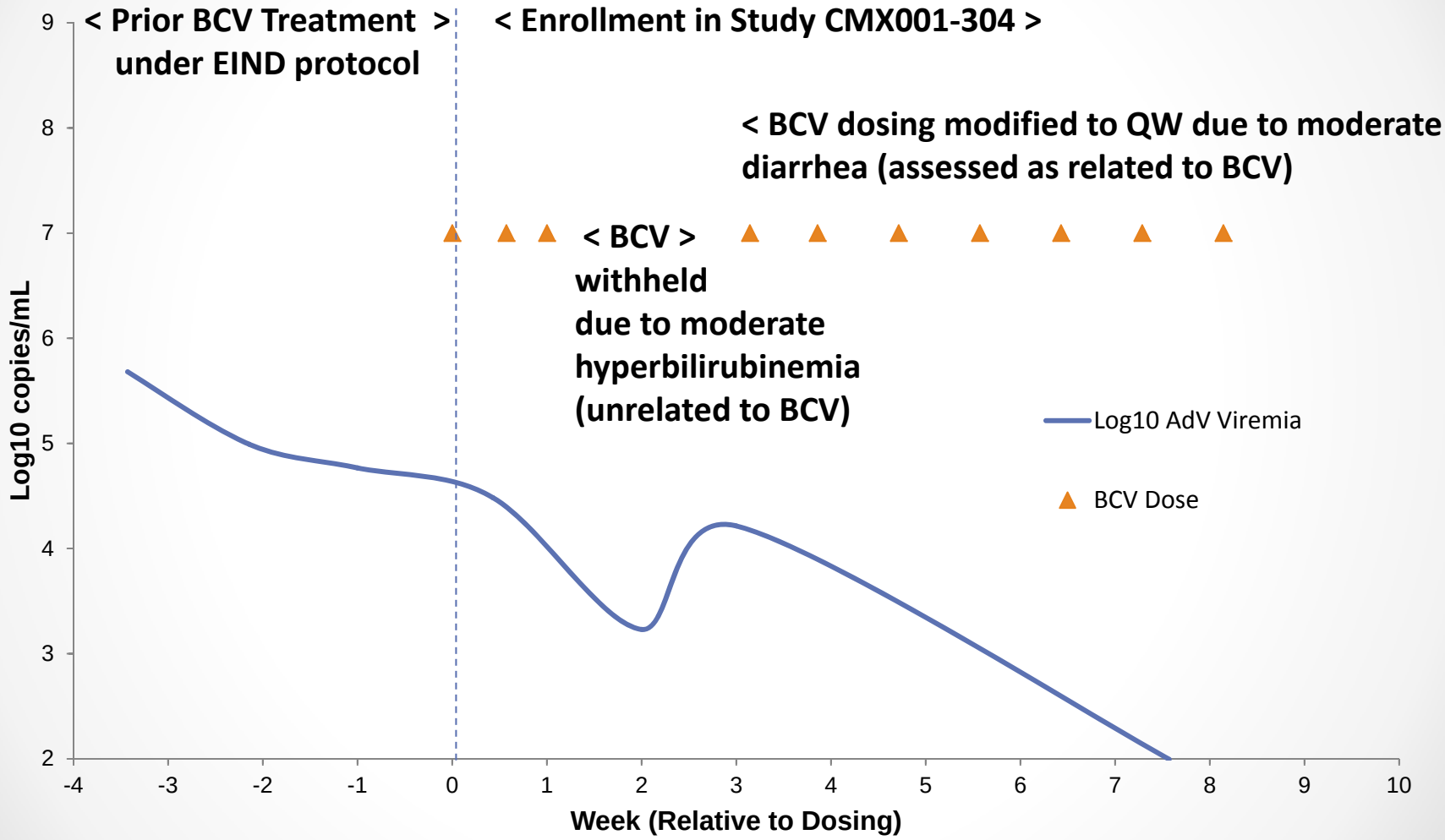
Change in Plasma AdV DNA over Time: All Subjects



← Subject received prior treatment with CDV, and had baseline T87I mutation, associated with resistance to CDV and BCV *in vitro*

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 > 2log$_{10}$ decline at last on-treatment.

Treatment Interruption



Strong Virologic Responses Observed with BCV

15/23 (65%) had ≥ 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%)
	≥ 4.0log_{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%)
	≥ 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%**)

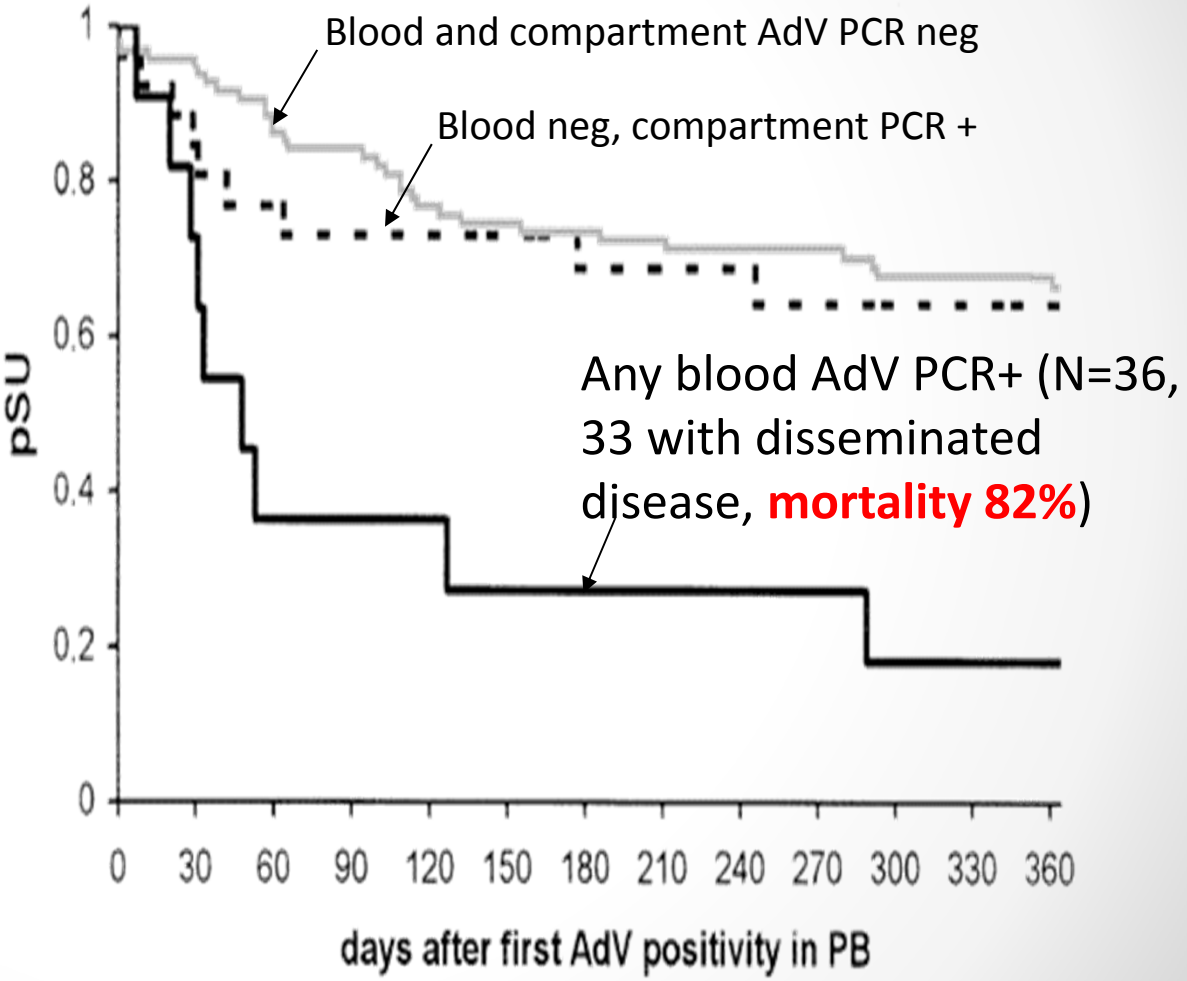
CMX001-304

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)[1]



[1] 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%[1-4]
  - 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**

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

Summary of Safety: Adverse Events

	Pediatrics (n = 20)	Adults (n = 6)	All (N = 26)
Subjects with ≥ 1 SAE	14 (70%)	6 (100%)	20 (77%)
Subjects with ≥ 1 fatal AE*	6 (30%)	1 (17%)	7 (27%)
Subjects with ≥ 1 **AE requiring treatment discontinuation**[#]	2 (10%)	1 (17%)	**3 (12%)**

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

[#] 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 ≥ 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. ~ 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