Preliminary Results from the AdVise Study Evaluating Brincidofovir (BCV, CMX001) for the Treatment of Disseminated and High-Risk Adenovirus (AdV) Infection

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Disclosure Statement

- Michael Grimley, MD, Associate Professor of Clinical Pediatrics, Bone Marrow Transplant and Immune Deficiency, Cincinnati Children's Hospital Medical Center
  - No disclosures

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Adenovirus: Epidemiology and Current Treatment Options

- Wide spectrum of presentation from asymptomatic viremia to severe and often disseminated disease
- Allogeneic hematopoietic cell transplant (allo HCT) recipients at greatest risk
- 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 site-specific risk factors (young age, receipt of T cell-depleted graft, mismatched or unrelated graft, cord blood, acute graft versus host disease, etc.)
- Current standard of care: supportive, reduction of immune suppression, and unproven antivirals (typically IV cidofovir [CDV] despite risk of significant renal injury)

Source: Lion T. Clin Microbiol Rev 2014:27(3):441-62

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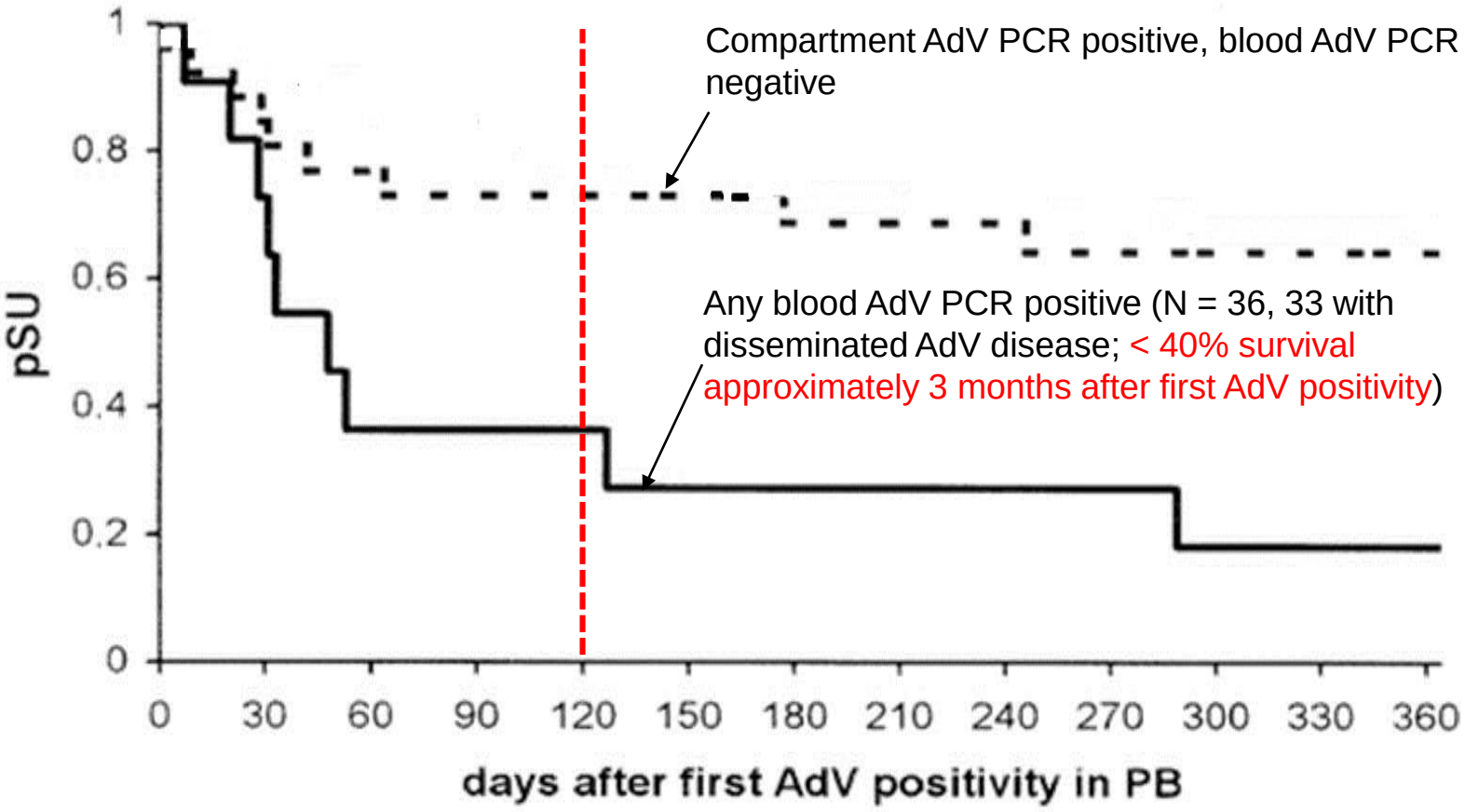
High Short-term Mortality in Patients with Disseminated Disease

Greater than 60% short-term mortality reported in a prospective, single center study in pediatric patients (Lion et al, 2003)



Source: Adapted from Lion T, et al. Blood 2003;102(3):1114-20

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Brincidofovir (BCV, CMX001)

- BCV is a lipid-conjugate of CDV, administered orally twice a week (BIW)
- In Phase 3 clinical development for prevention of cytomegalovirus (CMV) in allo HCT recipients and treatment of AdV
- Also in development as possible medical countermeasure for smallpox (under Animal Rule)
- *In vitro* activity against multiple dsDNA viruses
- Data from pilot part of Phase 3 AdVise (CMX001-304) trial (N = 48) presented at IDSA/ID Week September 2014*

*Young J-A, Grimley M, et al. ID Week 2014 Abstracts, Late Breaker Oral Abstract LB-3, Open Forum Infect Dis (Fall 2014) 1 (suppl 1): S66-9

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Safety Database of > 1000 Individuals To Date

- Lack of hematologic toxicity allows pre-engraftment dosing
- No nephrotoxicity – Not a substrate of kidney organ anion transporter 1 (OAT 1)
- Drug-related GI events manageable and not dose-limiting
- Non-adverse low-level ALT elevation observed in preclinical testing, without histopathology
- Asymptomatic elevations in serum aminotransferases manageable and not dose-limiting

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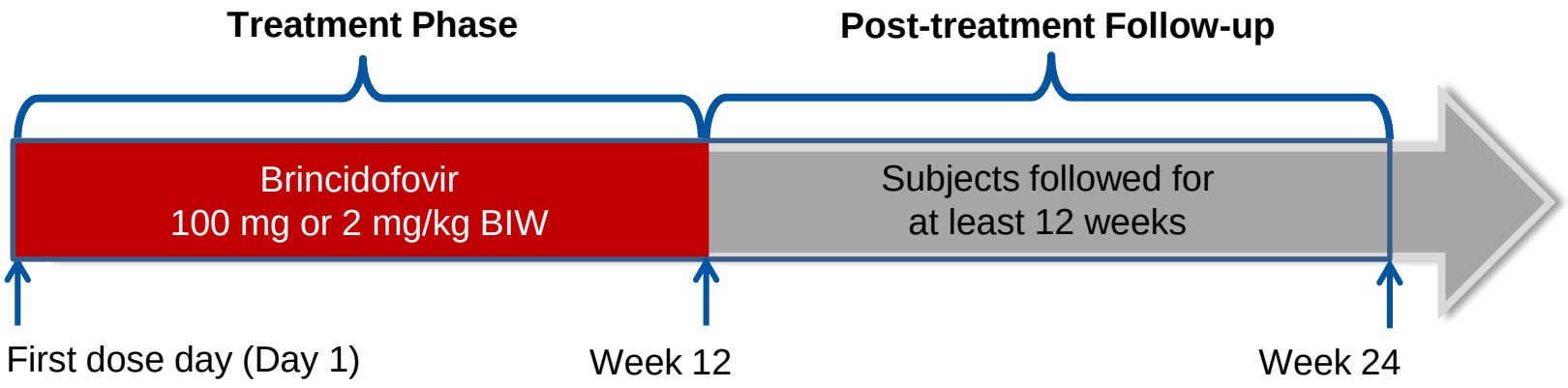
AdVise: Study Overview

- As of January 8, 2015, data available from 85 subjects enrolled across 20 study centers
  - Median 10 weeks of follow-up (range: 1 to 34)
- Open-label treatment for 12 weeks: 100 mg BIW (or 2 mg/kg BIW if < 50 kg)
  - Median treatment duration: 36 days (range: 1 to 167)



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Estimated AdV Incidence at AdVise Study Centers

- Pediatric patients: 11.5% (95% CI: 6.9 to 16.1)
- Adults: 4.8% (95% CI: 0.8 to 8.8)

  - Estimates based on actual AdVise enrollment and an estimate of the number of allo HCTs performed at AdVise study centers over enrollment period (from BMT Registry)
  - True incidences will likely be higher since not all AdV patients at each center are eligible for or agree to participate in AdVise

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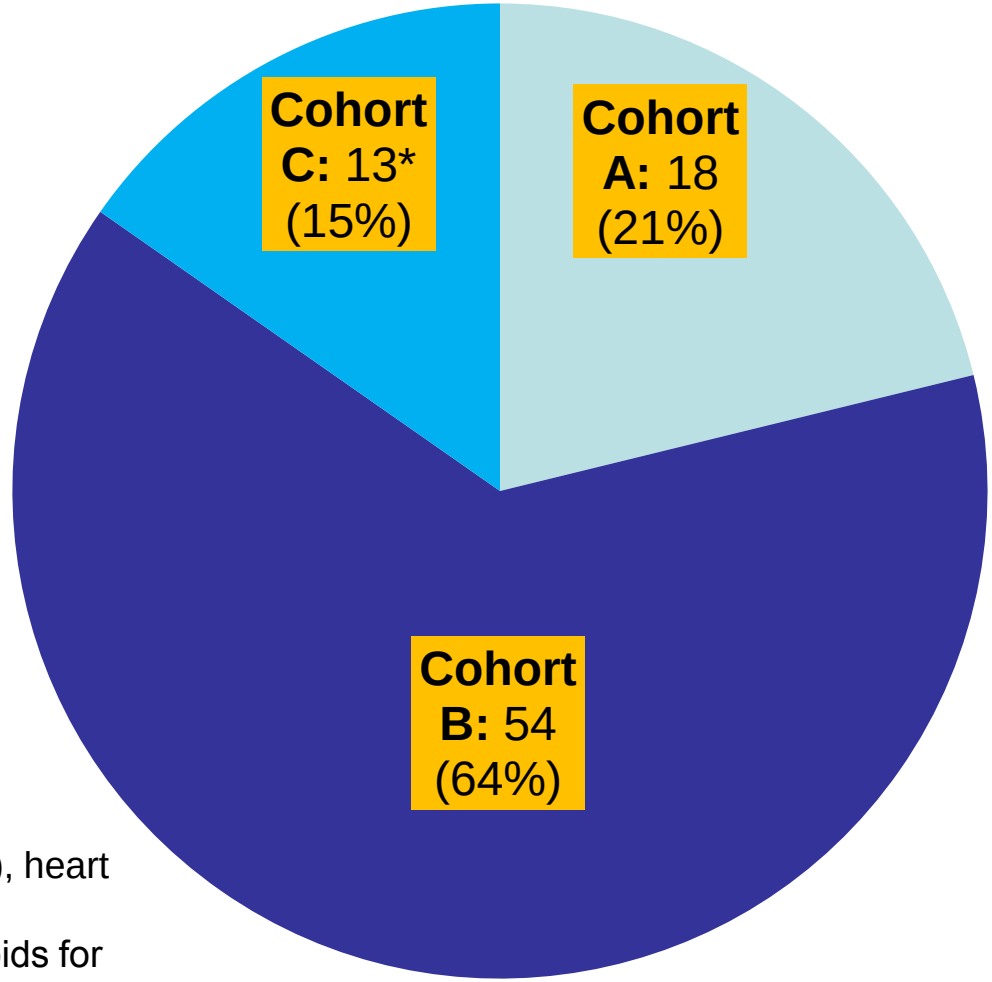
AdVise: Prospectively Defined Cohorts

Cohort A: Allo HCT patients at risk of AdV disease progression (defined as asymptomatic with plasma viral load [VL] ≥ 1000 c/mL or symptomatic in one organ system and plasma VL < 1000 c/mL)

Cohort B: Allo HCT patients with disseminated AdV disease (defined as symptomatic in one organ system with plasma VL ≥ 1000 c/mL or symptomatic in two or more organ systems)

Cohort C: All other (i.e., non-allo HCT) patients with disseminated AdV disease or at risk of AdV disease progression (as defined for Cohorts A and B)



*Includes 9 solid organ transplant recipients: liver/pancreas/small bowel (2), liver (2), lung (2), heart (1), kidney (1), small bowel (1); 3 chemotherapy patients, and one “other” (patient receiving steroids for fibromyalgia)

Ten subjects (77%) had disseminated AdV disease

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AdVise: Subject Demographics (N = 85)

Median Age (Range)	11 yrs (8 mo -69 yrs)
Age < 18 yrs (n [%])	59 (69%)
Male Sex (n [%])	56 (66%)
White Race (n [%])	62 (73%)

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AdVise: Baseline Viral Characteristics

AdV Detected by Compartment (n [%]):	Plasma	71 (84%)
	Urine	47 (55%)
	Stool	62 (73%)
	Respiratory secretions	39 (46%)
Baseline AdV Plasma Viremia ≥ 10^4 c/mL	All Subjects	39 (46%)
(n [%]):	Cohort A (n = 18)	2 (11%)
	Cohort B (n = 54)	32 (59%)
	Cohort C (n = 13)	5 (38%)
Prior Treatment with IV CDV (n [%])	Yes	32 (38%)
Co-infection with another dsDNA virus (n [%])*	Yes	50 (59%)

***Other dsDNA viruses:** 46% BK virus (BKV); 28% CMV, and 6% Epstein-Barr virus (EBV) detected by PCR at baseline

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AdVise: A Majority of Subjects Suppressed Plasma AdV DNA to Undetectable Levels

Plasma AdV DNA	Undetectable at Any Time On-treatment (n/N [%])	Undetectable at Last On-treatment Assessment (n/N [%])
All Subjects:	42 / 71 (59%)	36 / 71 (51%)
Cohort A (Asymptomatic or Localized):	8 / 11 (73%)	8 / 11 (73%)
Cohort B (Disseminated):	29 / 50 (58%)	23 / 50 (46%)
Cohort C (All Non-allo HCT):	5 / 10 (50%)	5 / 10 (50%)

- **Subjects with detectable AdV in plasma (n = 71):** Median change from baseline to nadir = -1.4 $\log_{10}$ c/mL (range: -8.0 to 0.6); 65% achieved ≥ 3 $\log_{10}$ decrease or to undetectable
- **Disseminated AdV, Cohort B (n = 50):** Median change from baseline to nadir = -1.9 $\log_{10}$ c/mL (range: -5.4 to 0.6); 66% achieved ≥ 3 $\log_{10}$ decrease or to undetectable

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AdVise: Clearance from Respiratory, Gastrointestinal and Genitourinary Compartments

	Proportion of Subjects Clearing Virus from (n/N [%]):		
	Respiratory Secretions	**Urine**	**Stool**
All Subjects	26 / 39 (67%)	25 / 47 (53%)	34 / 62 (55%)
Cohort A (Asymptomatic or Localized)	3 / 4 (75%)	3 / 6 (50%)	7 / 12 (58%)
Cohort B (Disseminated)	19 / 27 (70%)	20 / 35 (57%)	21 / 40 (53%)
Cohort C (All Non-allo HCT)	4 / 8 (50%)	2 / 6 (33%)	6 / 10 (60%)

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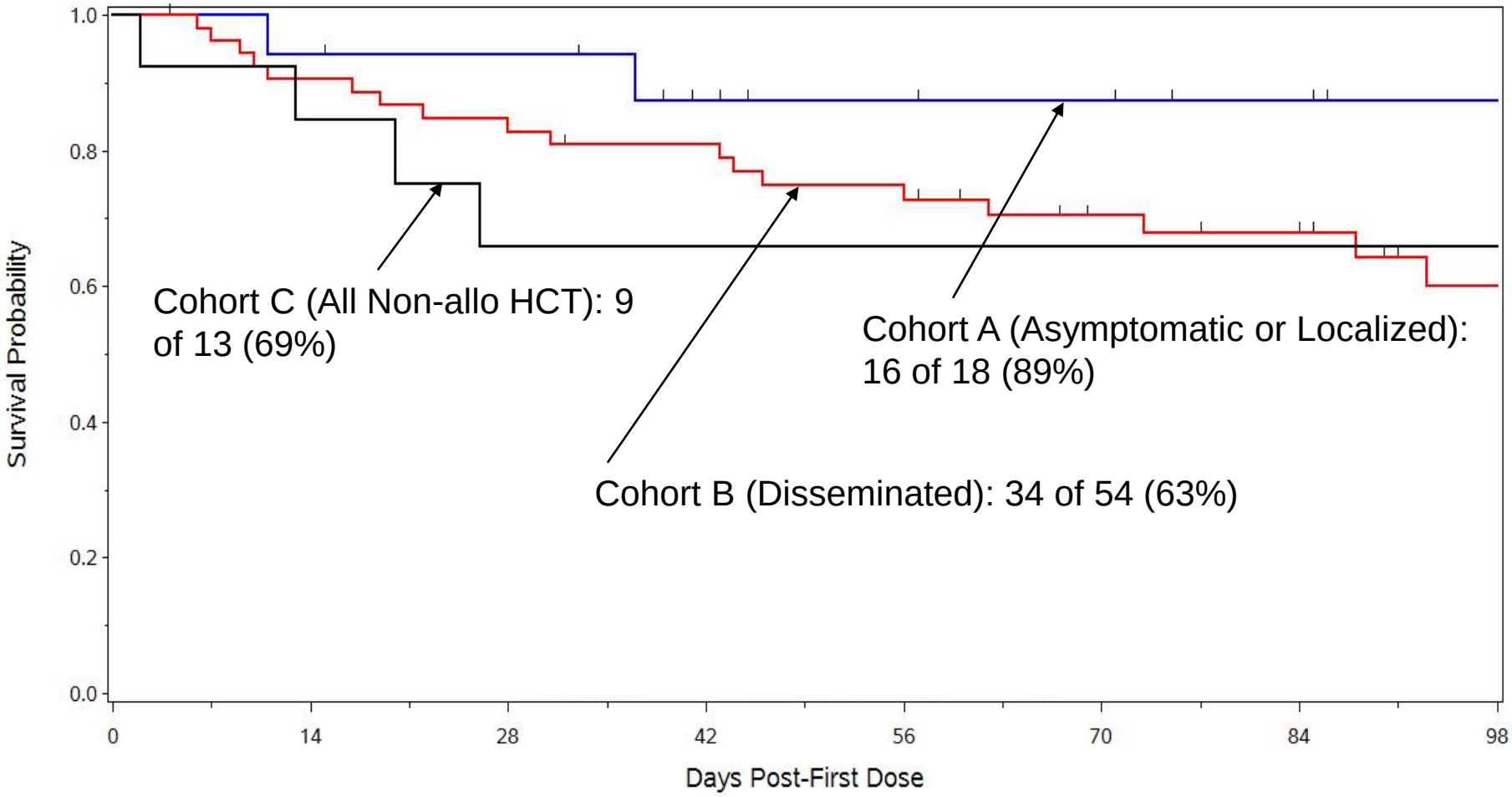
AdVise: Encouraging Short-term Survival in Allo HCT with Disseminated AdV Disease



Overall survival: 59 of 85 subjects (69%)

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AdVise: Few Discontinuations due to BCV-related Events

	Discontinuation Due to:	
	Any Adverse Event	BCV-related Adverse Event
All Subjects (N = 85)	14 (16%)	3* (4%)
Pediatrics (n = 59)	9 (15%)	1 (2%)
Adults (n = 26)	5 (19%)	2 (8%)
Cohort A (Asymptomatic or Localized; n = 18)	4 (22%)	1 (6%)
Cohort B (Disseminated; n = 54)	7 (13%)	1 (2%)
Cohort C (All Non-allo HCT; n = 13)	3 (23%)	1 (8%)

*Treatment-limiting AEs assessed as related to BCV were: abdominal pain (one adult in Cohort B), worsening diarrhea (one adult in Cohort C), and abdominal pain and diarrhea (in one pediatric subject in Cohort A)

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AdVise: Preliminary Conclusions

Among 85 subjects enrolled in AdVise to-date:

- 37% mortality among allo HCT subjects with disseminated disease after median follow-up of 75 days
  - Overall 31% mortality across all three treatment cohorts
- Majority of subjects had ≥ 3 $\log_{10}$ c/mL decline or undetectable AdV in plasma, and cleared AdV from respiratory, gastrointestinal, or genitourinary compartments
- Less than 5% of subjects (3 of 85) discontinued therapy due to a BCV-related event
- More than half of subjects enrolled had two or more dsDNA viral infections at study entry

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What Next for AdVise?

- Target enrollment in AdVise increased to ~ 200 patients (minimum 100 allo HCT with disseminated AdV disease)
- Survival and other outcomes in allo HCT in AdVise to be compared to historical outcomes in matched controls from the same medical centers
- Epidemiology of AdV and other dsDNA viruses (BKV, CMV, EBV, HHV-6, etc.) will be determined from banked samples at selected centers (Study CMX001-306)

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AdVise Study Centers and Investigators

- Children's Hospital of Los Angeles (Dr. Abdel-Azim)
- Stanford University Medical Center (Dr. Agarwal/Dr. Brown)
- Children's Hospital of Philadelphia (Dr. Bunin)
- MD Anderson Cancer Center (Dr. Chemaly)
- Levine Children's Hospital (Dr. Eckrich)
- University of Nebraska Medical Center (Dr. Florescu)
- Children's Hospital of Colorado (Dr. Giller)
- Children's Hospital of Pittsburgh/University of Pittsburgh Medical Center (Dr. Goyal)
- Cincinnati Children's Hospital Medical Center (Dr. Grimley)
- Children's Healthcare of Atlanta (Dr. Haight)
- Intermountain Healthcare (Dr. Hoda)
- Cook Children's Healthcare System (Dr. Howrey)
- Children's National Health System Center for Cancer and Blood Disorders (Dr. Jacobsohn)
- Johns Hopkins Hospital (Dr. Loeb/Dr. Boger)
- St. Jude Children's Research Hospital (Dr. Maron)
- Brigham and Women's Hospital (Dr. Marty)
- University of Chicago (Dr. Mullane)
- Baylor College of Medicine (Dr. Munoz-Rivas)
- Memorial Sloan Kettering (Dr. Papanicolaou)
- Duke University Medical Center (Dr. Prasad)
- Weill Cornell Medical College (Dr. Soave)
- Medical College of Wisconsin (Dr. Talano)
- Children's Mercy Hospital (Dr. Yin)
- University of Minnesota (Dr. Young)
- Children's Hospital of New Orleans (Dr. Yu)

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