Improved Outcomes in Allogeneic Hematopoietic Cell Transplant Patients Treated with Brincidofovir (CMX001, BCV) for Disseminated Adenovirus Disease Compared to Literature: Updated Preliminary Results from the AdVise (CMX001-304) Study

Michael Grimley, MD[1], Genovefa Papanicolaou, MD[2], Gabriela Marón, MD[3], Greg Chittick[4], Thomas Brundage, MS[4], Andrew Bae[4], Hervé Momméja-Marin, MD[4], W. Garrett Nichols, MD[4], Vinod K. Prasad, MD[5]

[1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [2]Memorial Sloan-Kettering Cancer Center, New York, NY; [3]St. Jude Children's Research Hospital, Memphis, TN; [4]Chimerix, Inc., Durham, NC; [5]Duke University Medical Center, Durham, NC

Disclosure Statement

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

Cincinnati Children's

Adenovirus: Epidemiology and Current Treatment Options

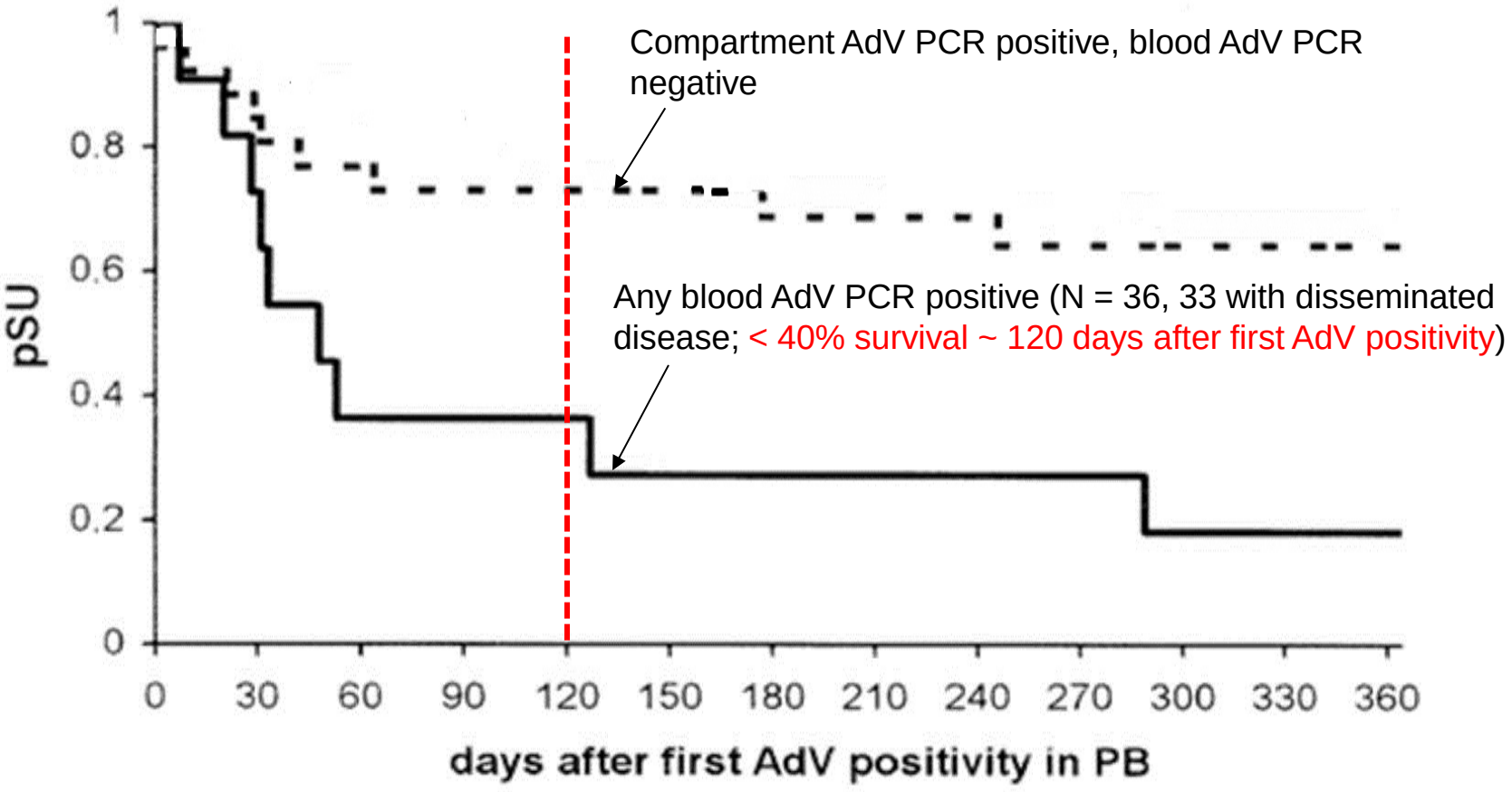
- Wide spectrum of presentation from asymptomatic viremia to severe and often disseminated disease
- Allogeneic (allo) HCT recipients at greatest risk
- Mortality reported to be up to 80% for allo HCT recipients with disseminated AdV disease*
- 5 to 50% incidence of infection in allo HCT recipients
  - Dependent on risk factors such as 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

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

Cincinnati Children's

High Short-term Mortality with Disseminated AdV Disease

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



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

Cincinnati Children's

Brincidofovir (BCV, CMX001)

- BCV is a lipid-conjugate of CDV, administered orally twice-weekly (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
- Preliminary data from Phase 3 AdVise trial (N = 48 subjects) presented at IDSA/IDWeek September 2014*

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

Cincinnati Children's

Safety Database of > 1000 Individuals To Date

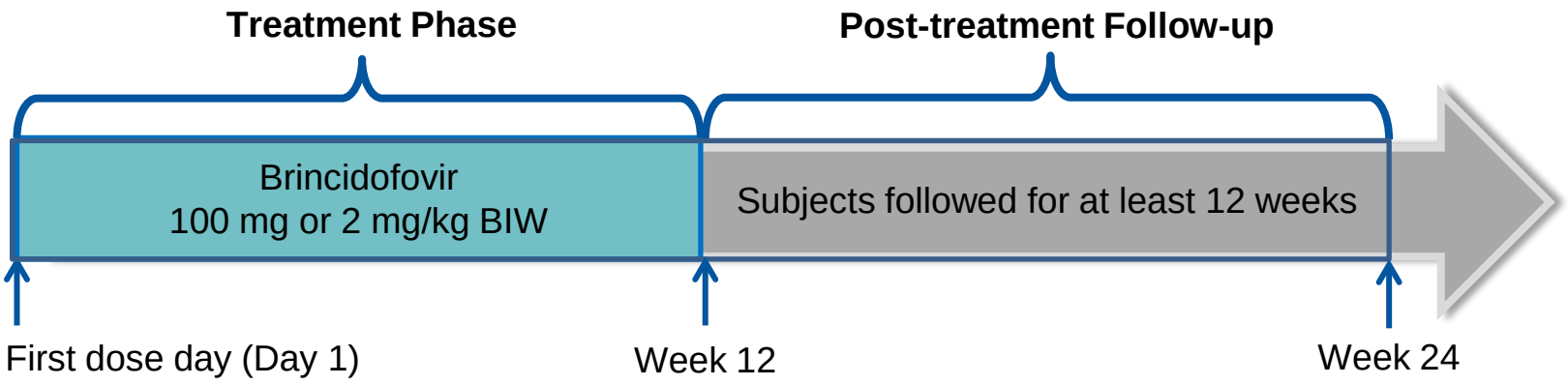
- Lack of hematologic toxicity allows pre-engraftment dosing
- No nephrotoxicity; not a substrate of kidney human organic anion transporter 1 (hOAT 1)
- Drug-related GI events manageable and not dose-limiting
- Non-adverse low-level ALT (SGPT) elevation observed in preclinical testing, without histopathology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

Cincinnati Children's

AdVise: Study Overview

- All subjects receive 12 wks of open-label treatment with BCV 100 mg BIW (or 2 mg/kg BIW if weight < 50 kg)

- Rescue BCV therapy (up to 12 additional wks treatment) available for relapse during follow-up



Cincinnati Children's

AdVise: Prospectively Defined Cohorts

<u>Cohort A</u>: Allo HCT patients "at risk of AdV disease progression"

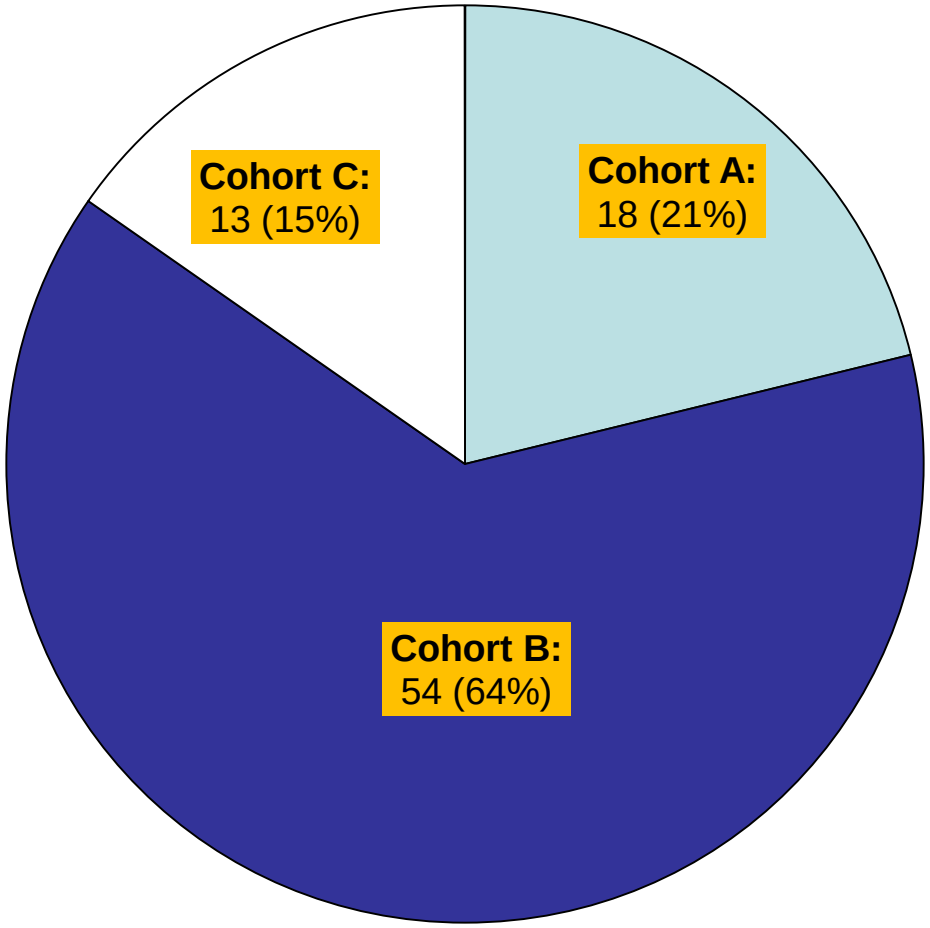
(EITHER asymptomatic with plasma AdV ≥ 1000 c/mL OR symptomatic in one organ system and plasma AdV < 1000 c/mL)

<u>Cohort B</u>: Allo HCT patients with "disseminated AdV disease"

(EITHER symptomatic in one organ system with plasma AdV ≥ 1000 c/mL OR symptomatic in two or more organ systems)

<u>Cohort C</u>: All other patients

(Solid organ transplant recipients, chemotherapy patients, etc. with disseminated AdV disease or at risk of AdV disease progression as defined for Cohorts A and B)



Cincinnati Children's

AdVise: Subject Demographics (Cohort B; N= 54)

Median Age (Range):	12 yrs (8 mos to 69 yrs)
Age < 18 yrs (n [%]):	34 (63%)
Male Sex (n [%]):	36 (67%)
White or Caucasian Race (n [%]):	40 (74%)

Cincinnati Children's

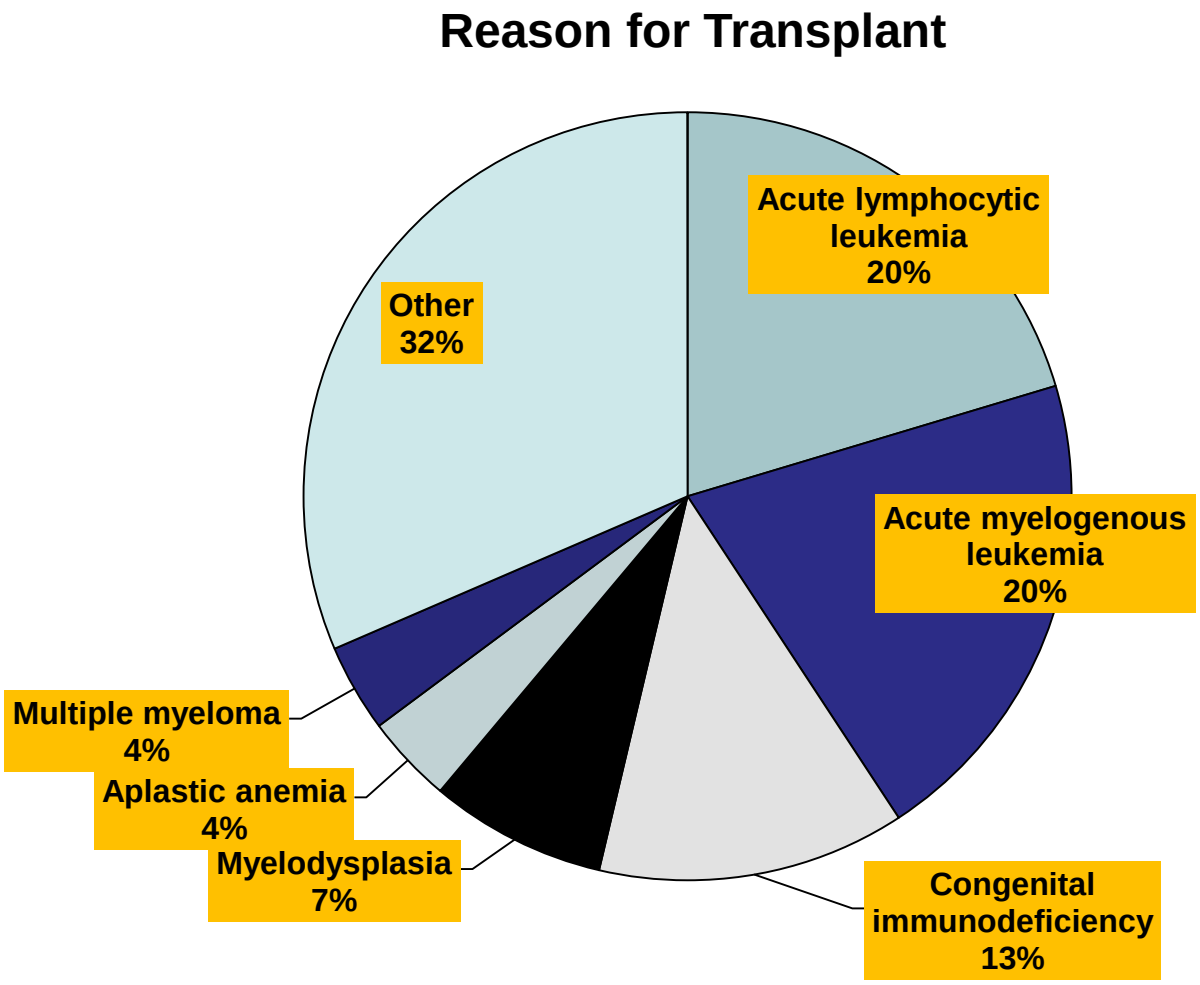
AdVise: Baseline Characteristics (Cohort B)

- Median date treatment initiated after HCT = 77 days (range: -1 to 2236)
- Median absolute lymphocyte count = 0.35 K/μL (range: 0 to 2.47; n = 36*)
- One third (18 of 54) had ongoing GvHD at enrollment
  - Including 19% (10 / 54) with GvHD of intestine
- Prior treatment with IV CDV reported in 41% (22 / 54)

* Centralized safety laboratory reporting not available at study initiation; TLTC (too low to count) values imputed as zero

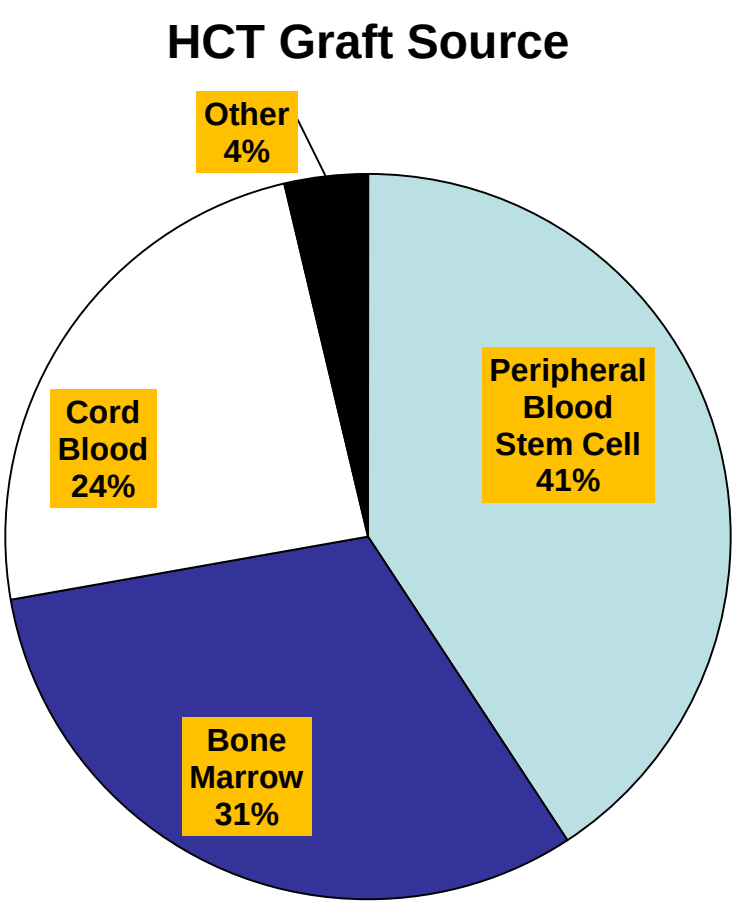
Cincinnati Children's

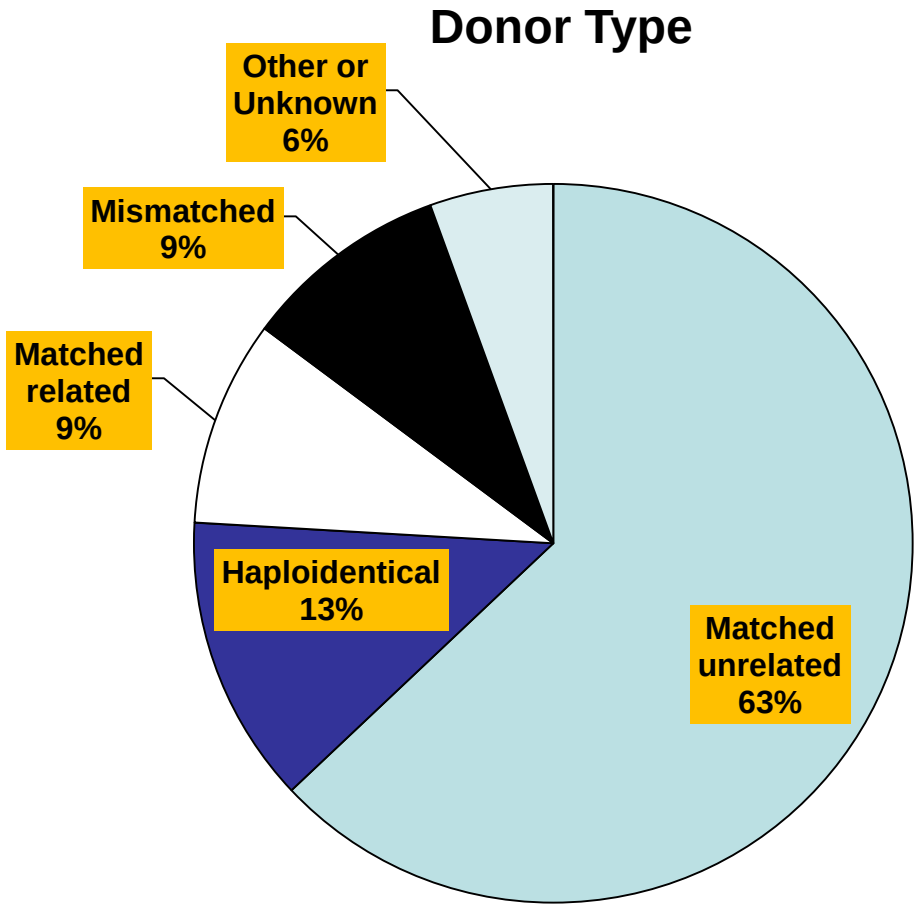
AdVise: Reason for Transplant (Cohort B)



Cincinnati Children's

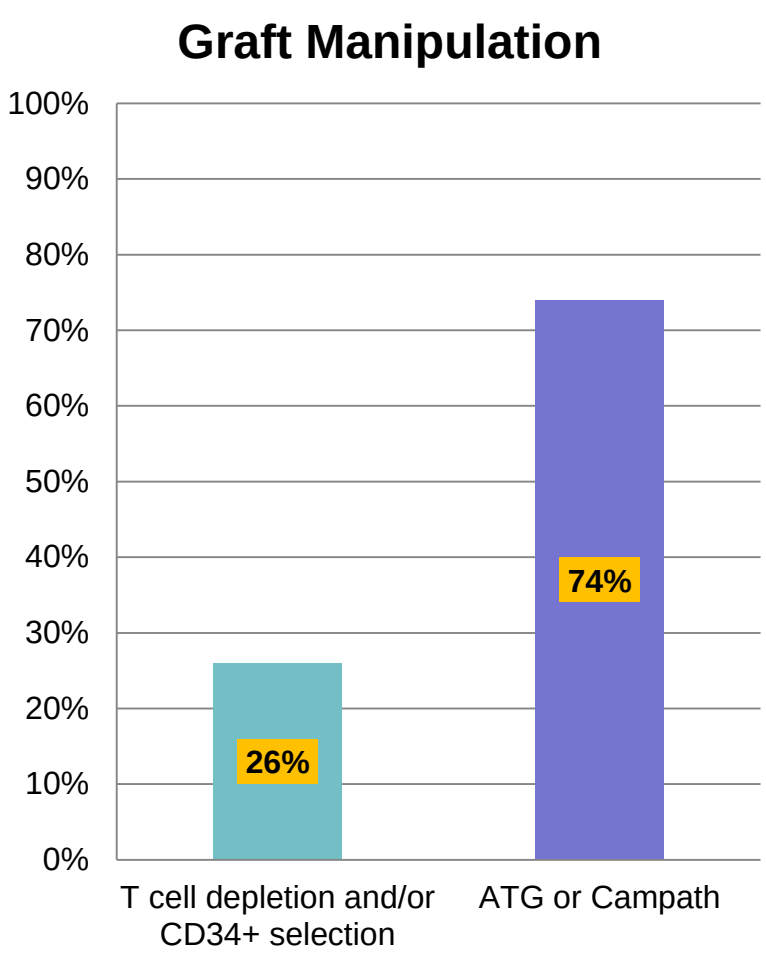
AdVise: HCT Graft Source & Donor Type (Cohort B)

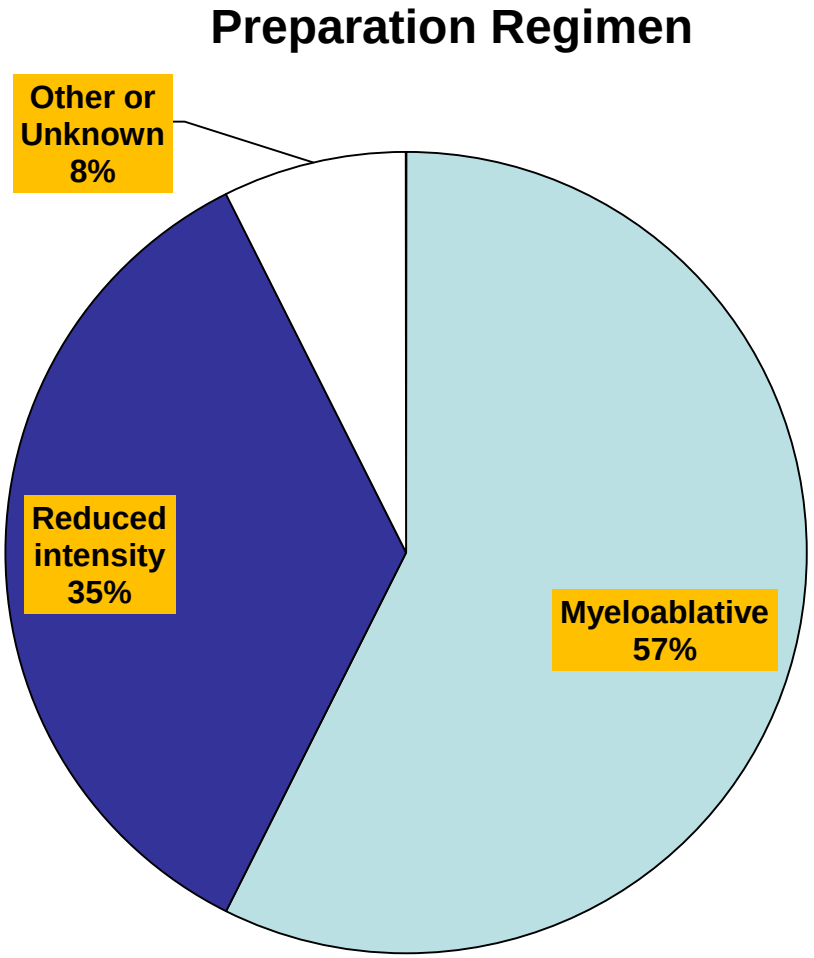




Cincinnati Children's

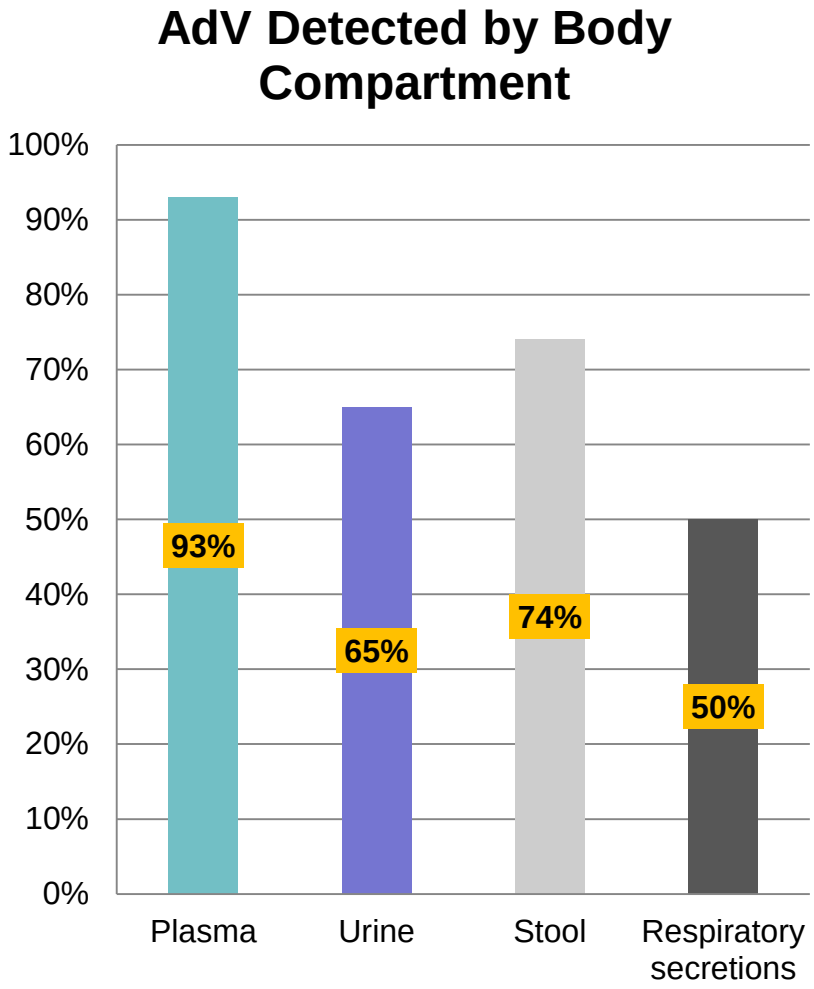
AdVise: Graft Manipulation & Preparation Regimen (Cohort B)

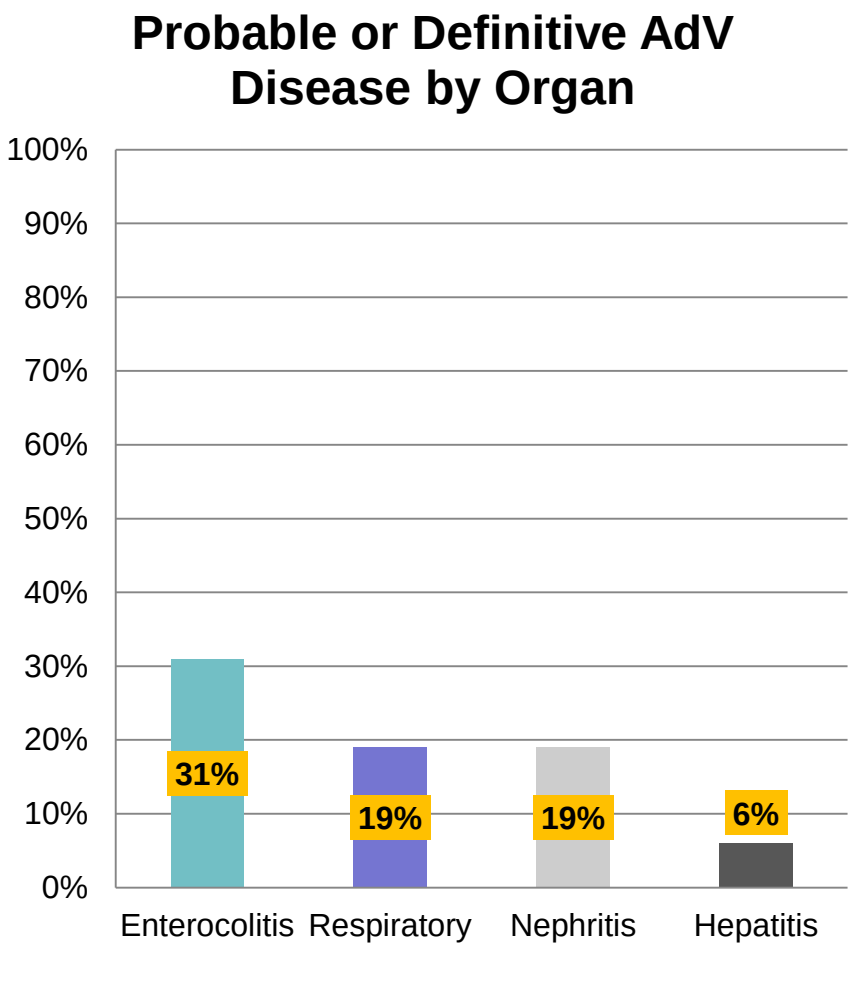




Cincinnati Children's

AdVise: AdV Disease Characteristics (Cohort B)



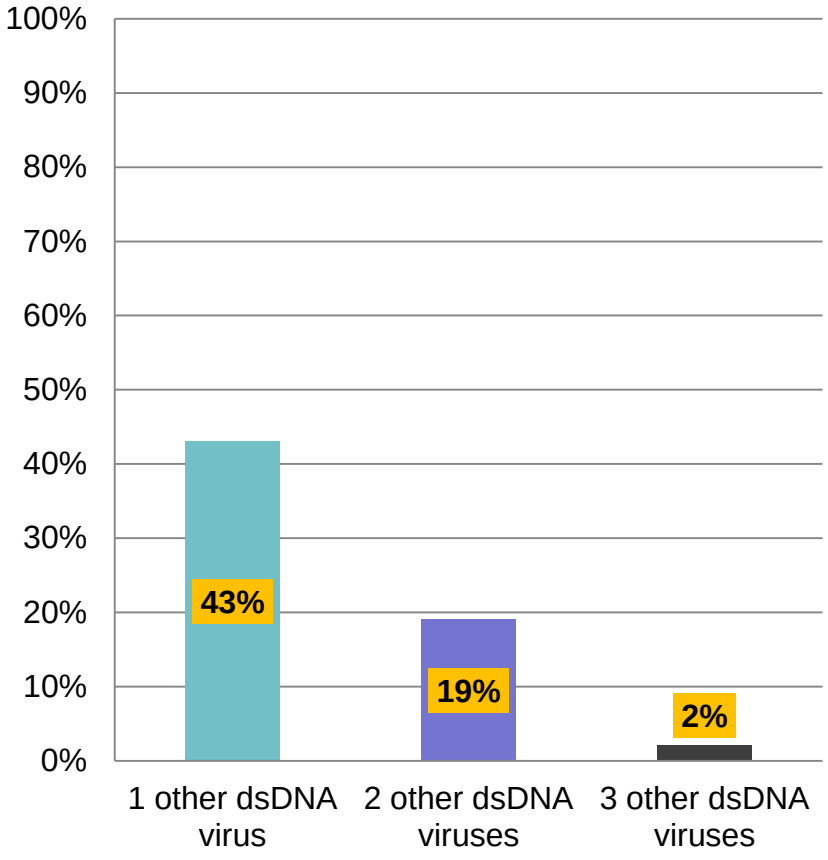


- Median plasma AdV viremia at baseline: 4.5 $\log_{10}$ copies/mL (range: not detected to 7.6)

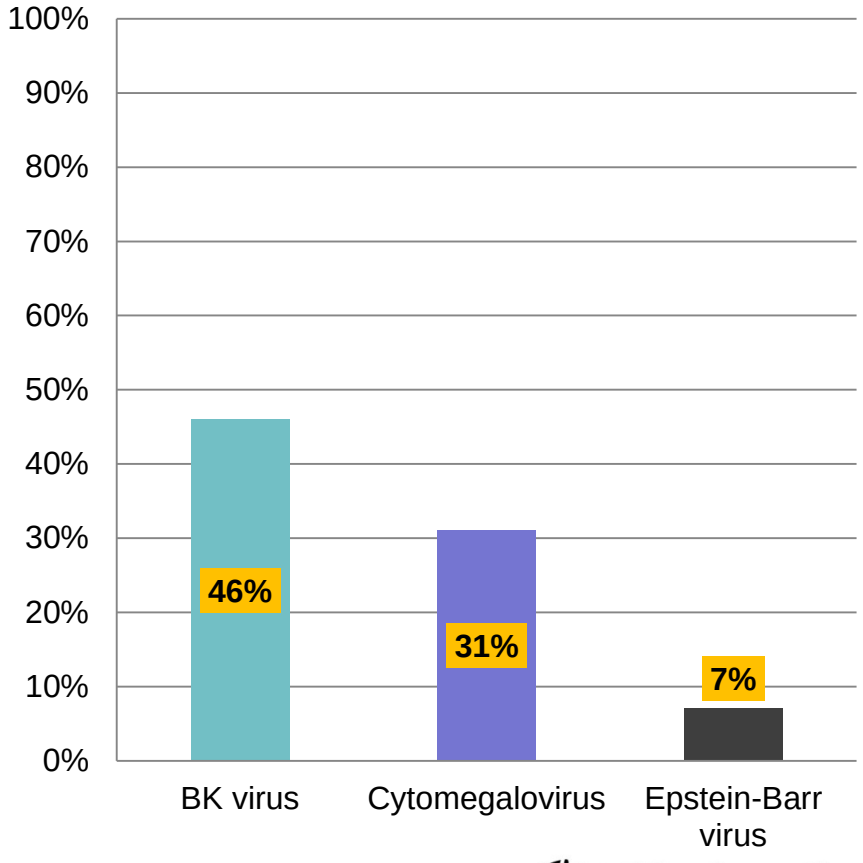
Cincinnati Children's

AdVise: Co-infection with Other dsDNA Viruses (Cohort B)

Subjects Co-infected with AdV and Other dsDNA Viruses



Other dsDNA Virus Co-infections



Cincinnati Children's

AdVise: Cohort B Median Treatment/Follow-up

- As of 8 January 2015, data available from 85 subjects
  - 54 allo HCT recipients with disseminated AdV disease enrolled in Cohort B across 17 study centers
- Median 11 weeks of follow-up (range: 1-34)
- Median treatment duration: 39 days (range: 1-167) or 12 doses (range: 1-48)
  - Treatment extended for > 12 wks in 7 subjects

Cincinnati Children's

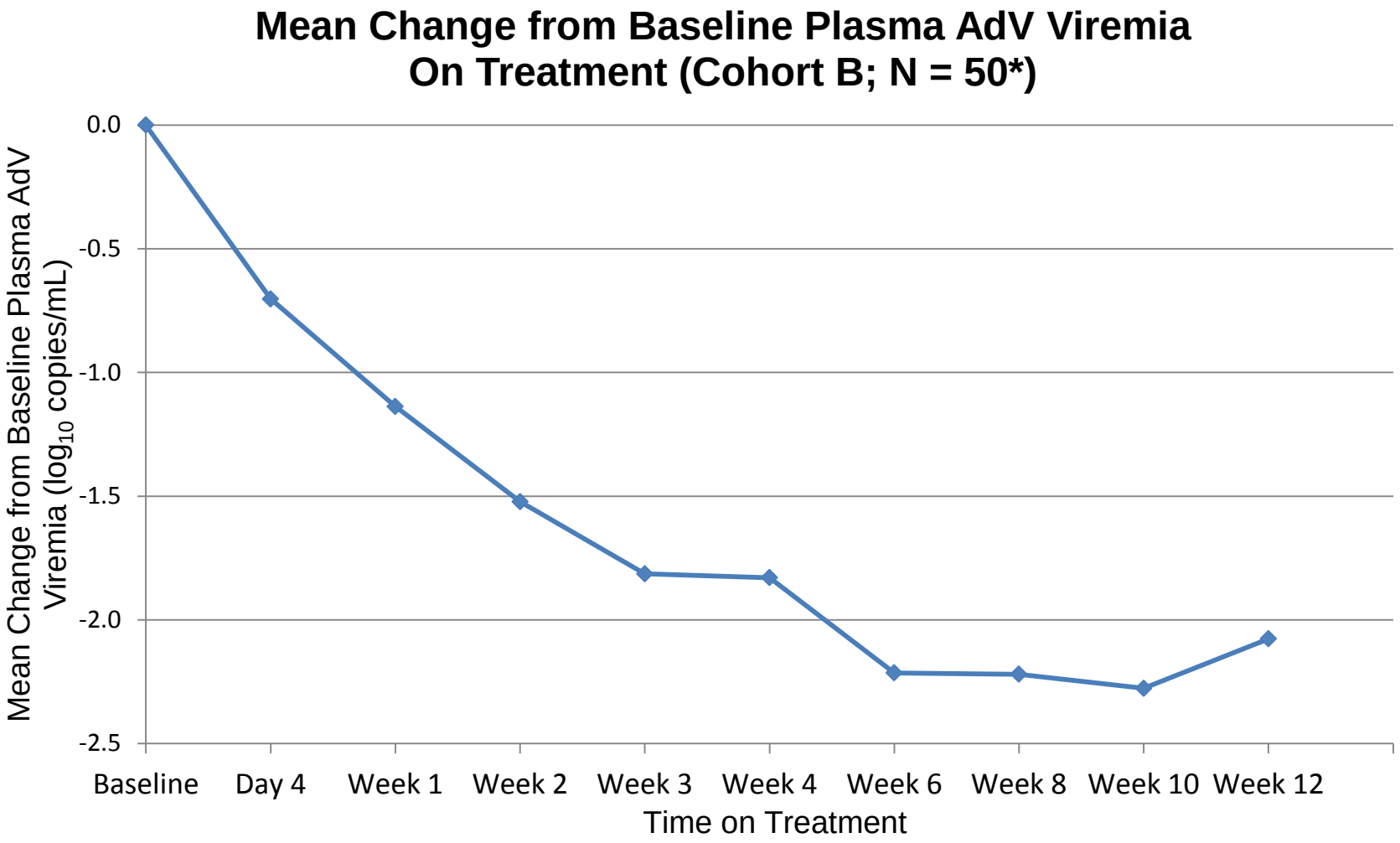
AdVise: Virologic Responses in Disseminated AdV Disease (Cohort B; N = 50*)

Subjects with plasma AdV undetectable any time on treatment (n [%]):	29 (58%)
Subjects with plasma AdV undetectable at end of treatment (n [%]):	23 (46%)
Median (range) time to minimum plasma AdV on treatment (days):	15 (3 to 106)
Subjects with ≥ 3 $\log_{10}$ copies/mL decrease or to undetectable (n [%]):	33 (66%)

* Subjects with detectable plasma AdV viremia at baseline

Cincinnati Children's

AdVise: Change in Plasma AdV Viremia on Treatment (Cohort B)

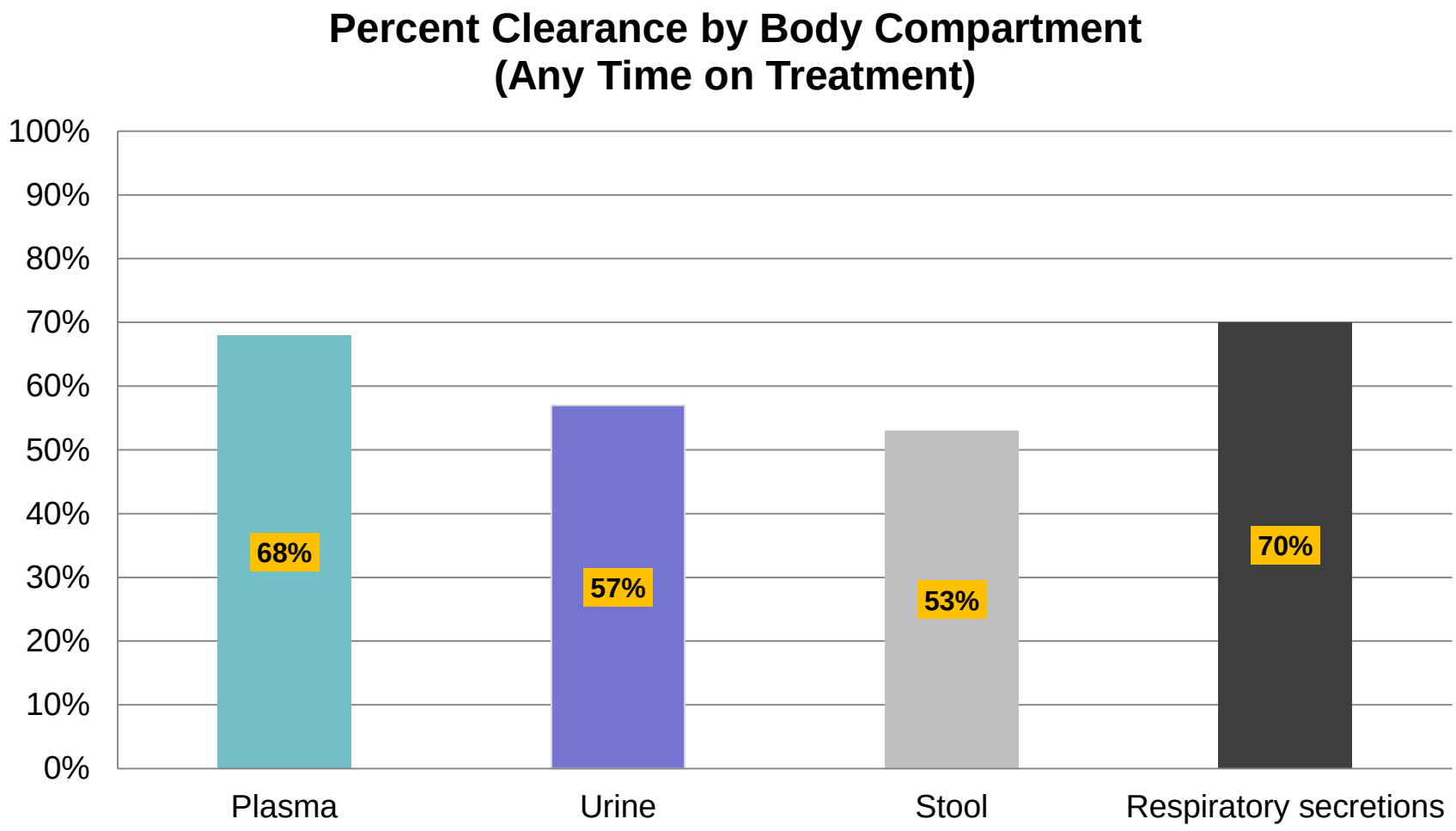


N =	50	39	44	38	35	29	26	21	16	13

* Subjects with detectable plasma AdV viremia at baseline

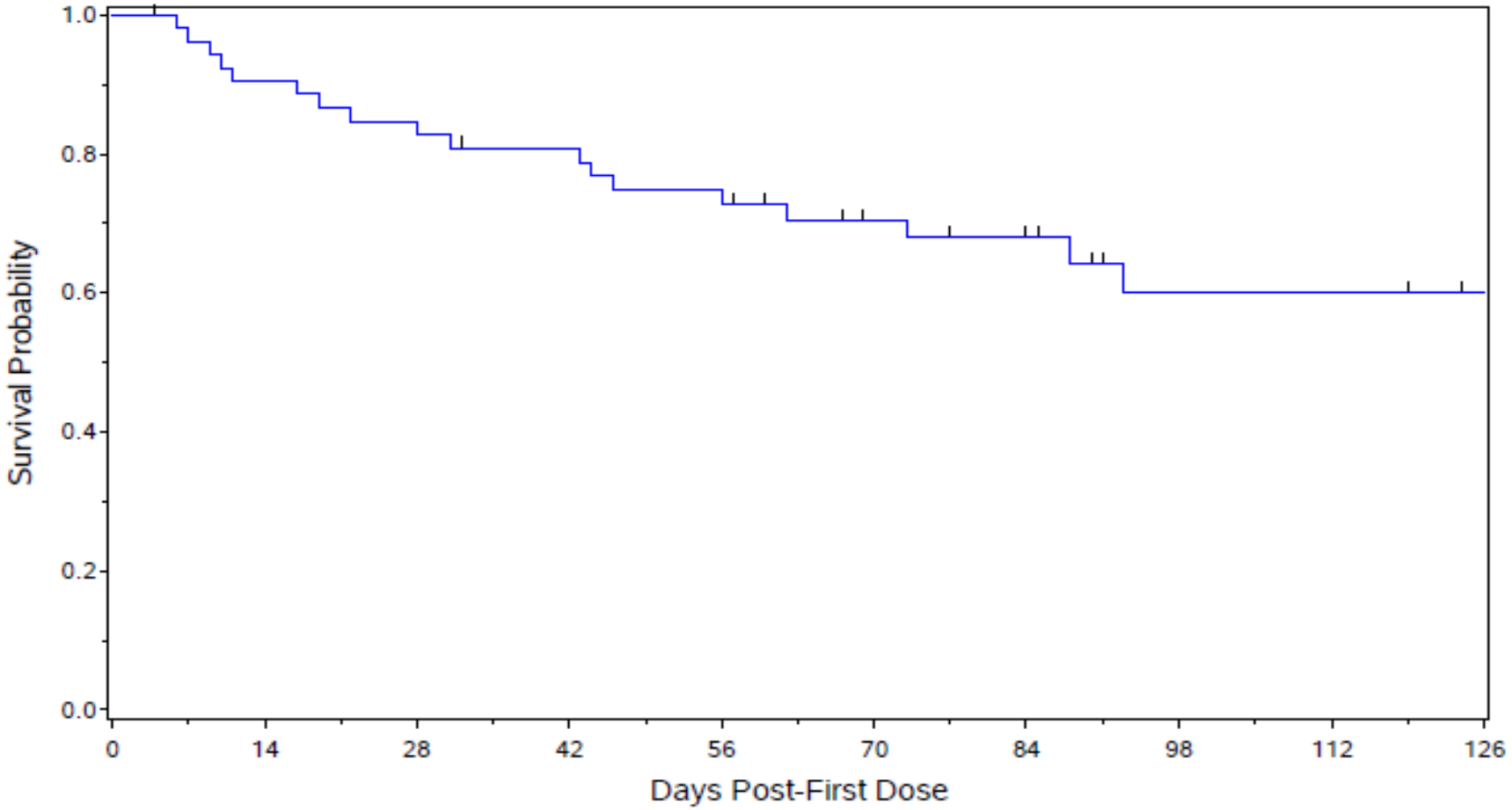
Cincinnati Children's

AdVise: Clearance of AdV from Body Compartments



Cincinnati Children's

AdVise: Encouraging Short-term Survival in Allo HCT with Disseminated AdV Disease (Cohort B)



Survival in Cohort B: 34 of 54 (63%) allo HCT recipients with disseminated AdV disease with median follow-up of 85 days for living subjects

Cincinnati Children's

AdVise: Preliminary Safety in Allo HCT with Disseminated AdV Disease (Cohort B)

- Among 20 deaths reported in Cohort B, none of the fatal adverse events (AEs) was assessed as related to BCV

- Among 7 subjects in Cohort B who were discontinued from BCV due to AE(s), only one event (Grade 2 abdominal pain in one subject) was assessed as related to BCV

Cincinnati Children's

AdVise: Preliminary Conclusions in Allo HCT with Disseminated AdV Disease (Cohort B)

Among 54 subjects enrolled in Cohort B with disseminated AdV disease to-date:

- 37% mortality after median follow-up of 75 days
  - compares to literature rates of up to 50 to 80% mortality

- Majority had ≥ 3 $\log_{10}$ c/mL decline or undetectable AdV in plasma, and cleared AdV from respiratory, GI, or genitourinary compartments

- Only one subject discontinued therapy due to a BCV-related event (Grade 2 abdominal pain)

- Almost two-thirds (63%) of subjects co-infected with one or more other (non-AdV) dsDNA viral infections at study entry

Cincinnati Children's

What Next for the AdVise Trial?

- Target enrollment in AdVise (CMX001-304) 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 control patients from same medical centers (Study CMX001-305)
- Epidemiology of AdV and other dsDNA viruses (BKV, CMV, EBV, HHV-6, etc.) will be determined from banked samples at selected centers

Cincinnati Children's

AdVise Study Centers and Investigators

The authors are grateful to the study participants and their families and to the following study centers (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 (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)

Cincinnati Children's