



ROLE OF ADENOVIRUS SPECIES AND TYPE ON VIROLOGIC RESPONSE TO BRINCIDOFOVIR

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Adenovirus: Epidemiology and Treatment Options

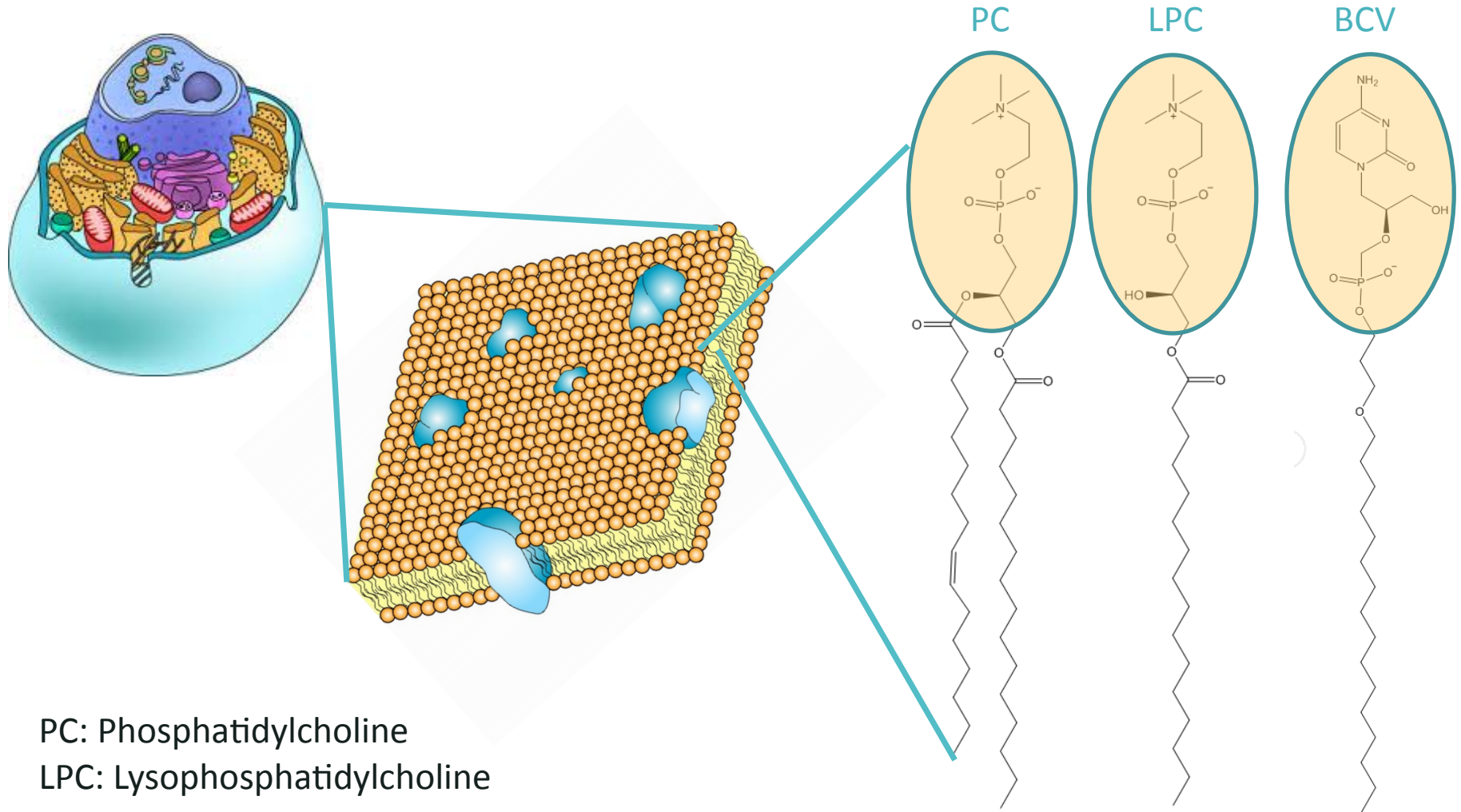
- Nonenveloped, double-stranded DNA viruses, genomes ranging from 34-37kbs
 - Divided into 7 major species (A-G)
 - >60 distinct types
- Allogeneic hematopoietic cell transplant (allo HCT) recipients are at greatest risk of severe disease, but AdV infection is a potential issue in any significantly immunosuppressed patient
- Mortality up to 80% reported for allo HCT recipients with disseminated AdV disease
- 5 to 50% incidence of reported infection in allo HCT appears to be dependent on multiple risk factors (age, graft type, unrelated graft, etc.)
- Current standard of care: supportive, reduction of immune suppression, and unproven antivirals (typically IV cidofovir)

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

Brincidofovir (BCV, CMX001)

- Active against all five families of dsDNA viruses *in vitro*
- Oral delivery
- No evidence of kidney or bone marrow toxicity detected in > 1,000 subjects receiving BCV
- Completed clinical trials:
 - HALT (CMX001-202) for AdV preemption
 - CMX001-201 & 301(SUPPRESS) for CMV prevention in HCT
- Ongoing clinical trials:
 - AdVise (CMX001-304) for AdV treatment in immunocompromised patients
 - Animal efficacy studies for smallpox (biodefense)

Brincidofovir Mimics Natural Phospholipids



BCV Inhibits Adenovirus (AdV) Replication *In Vitro*

| Adenovirus Serotype | BCV EC₅₀ (μM) | CDV EC₅₀ (μM) |
|----------------------------|---------------------------------|---------------------------------|
| AdVA31 | 0.020 | 1.4 |
| AdVB7 | 0.020 | 1.3 |
| AdVC1 | 0.006 | N.D. |
| AdVD8 | 0.027 | 1.0 |
| AdVE4 | 0.007 | N.D. |
| AdVF40 | 0.006 | N.D. |

Source: Data generated at Chimerix

Clinical Trials Where BCV Was Used to Treat AdV

- **Expanded Access Study (CMX001-350)**

- Patients with an immediately life-threatening or serious disease or condition caused by CMV, ADV, HSV, VAVC, VARV and/or monkeypox virus

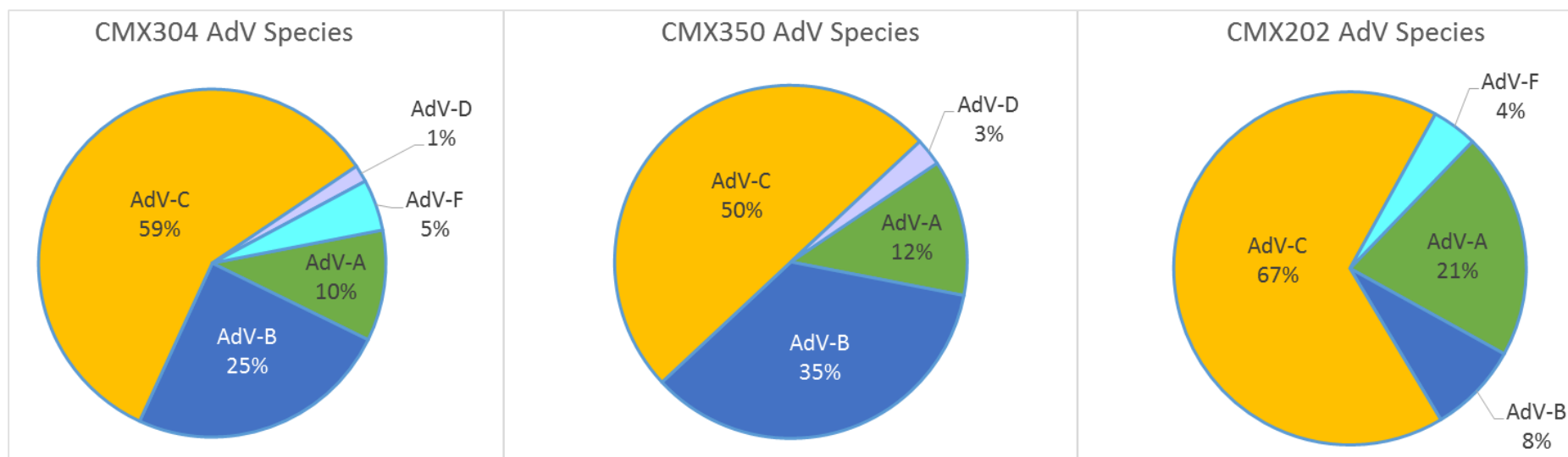
- **HALT (CMX001-202)**

- Hematopoietic stem cell transplant (HCT) recipients with asymptomatic AdV viremia (≥ 100 DNA copies/mL) stratified based on absolute lymphocyte count at screening (ALC; < 300 or ≥ 300 cells/mm³)
- Randomized to once-weekly (QW) BCV, twice weekly (BIW) BCV, or placebo

- **AdVise (CMX001-304)**

- Open-label oral dosing for 12 weeks: 100 mg BIW or 2 mg/kg BIW if < 50 kg
 - Cohort A: Allo HCT patients with asymptomatic or single-organ AdV disease
 - Cohort B: Allo HCT patients with disseminated AdV disease
 - Cohort C: Other (i.e., non-allo HCT) immunocompromised patients with disseminated AdV disease or limited AdV disease

Frequency of Adenovirus (AdV) Species in Plasma from 197 Patients Treated with BCV

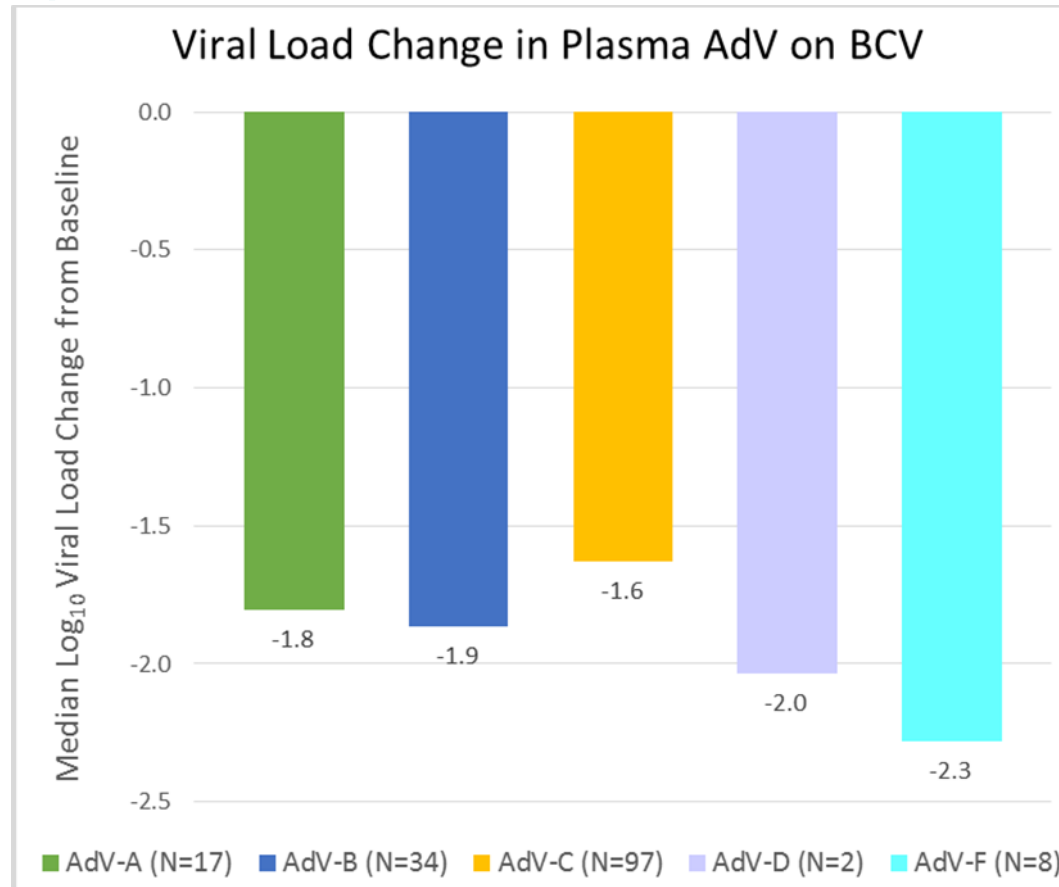


CMX-304 = 121

CMX-350 = 34

CMX-202 = 42

Virologic Response at Last Time on BCV Therapy by AdV Species (All Trials; 158 AdV Species in 148 Patients)

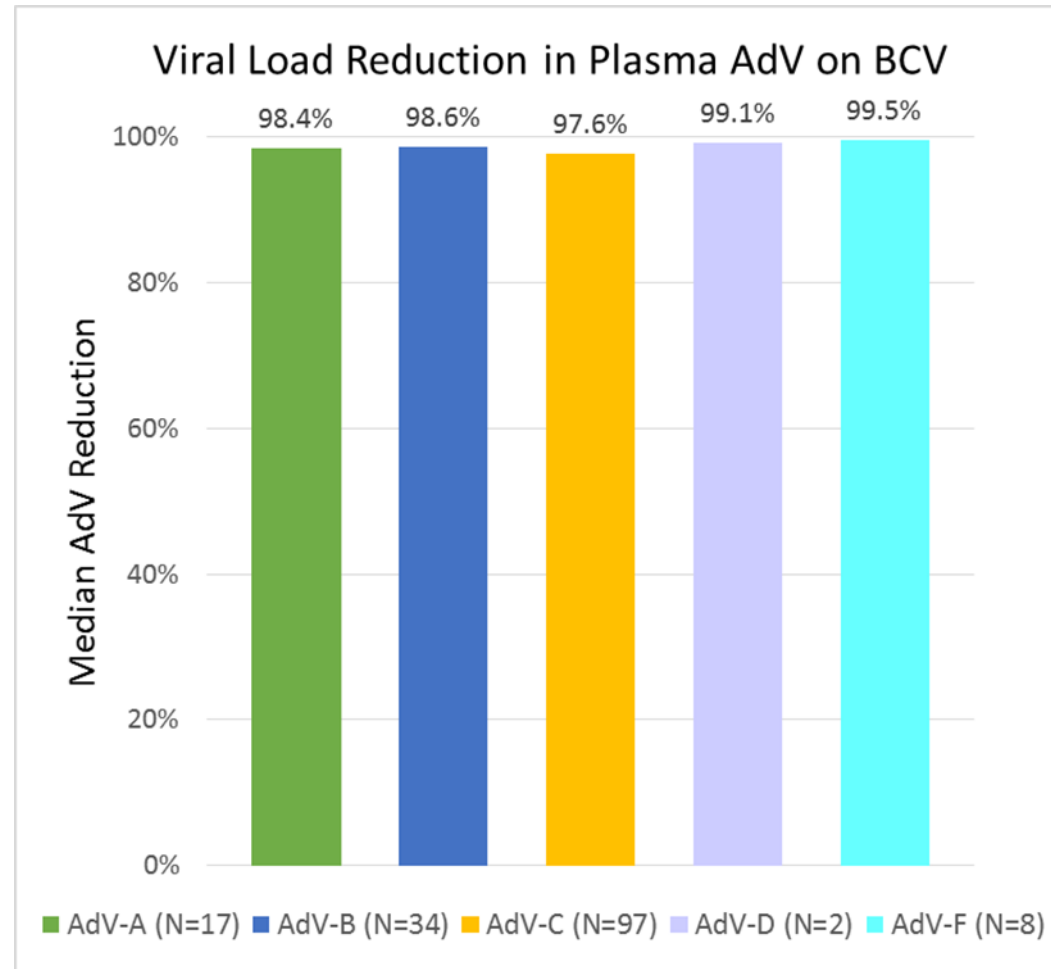


Patients (N=148) with detectable baseline viremia and at least 2 weeks of treatment with BCV were assessed at the last timepoint on BCV therapy

6 Patients harbored 2 different AdV species in plasma
2 Patients harbored 3 different AdV species in plasma

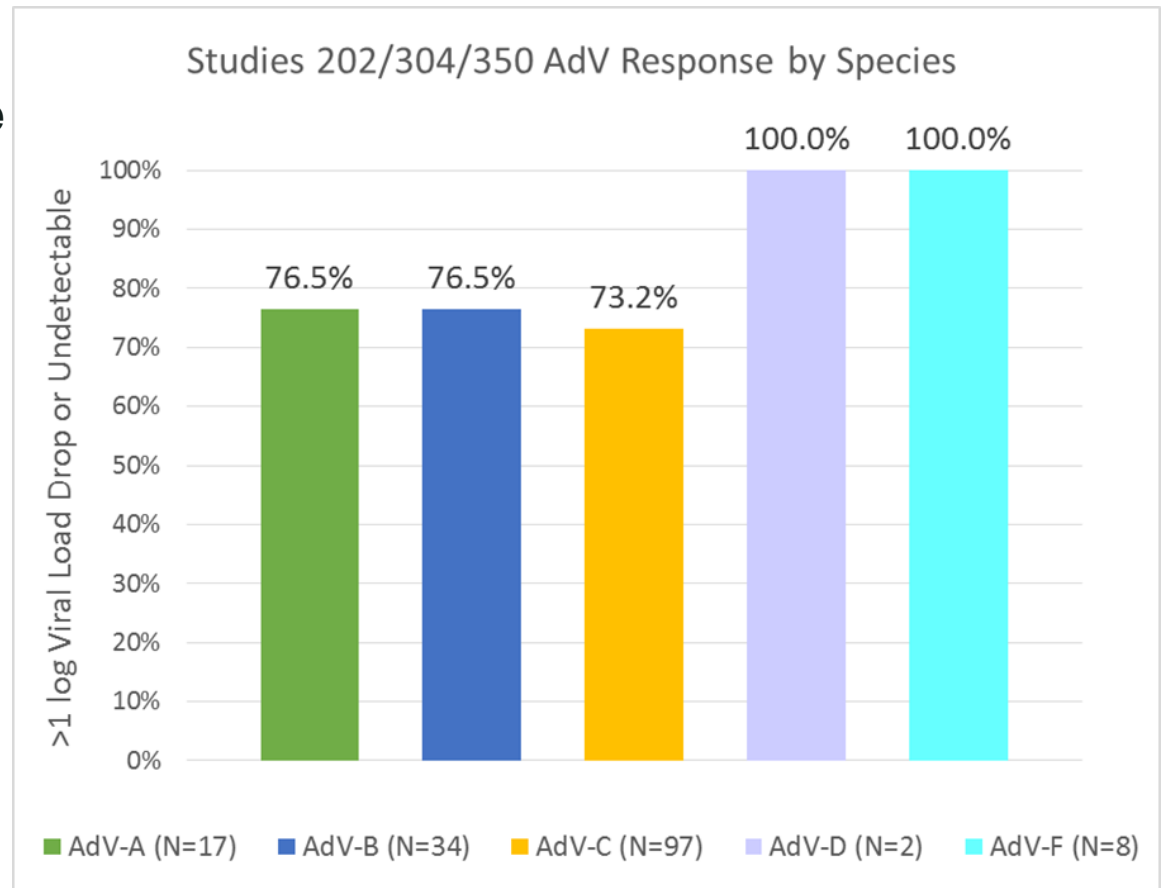
BCV: Antiviral Activity Against AdV

- Consistent decreases in AdV plasma viral load were observed in patients who received ≥ 2 weeks of BCV for AdV infection
 - >97% median AdV viral load reduction across AdV species



Virologic Response by Species (Combined Trials)

- The majority of patients had a 1 log drop or undetectable plasma AdV at the last timepoint on BCV



AdVise: Preliminary Data*

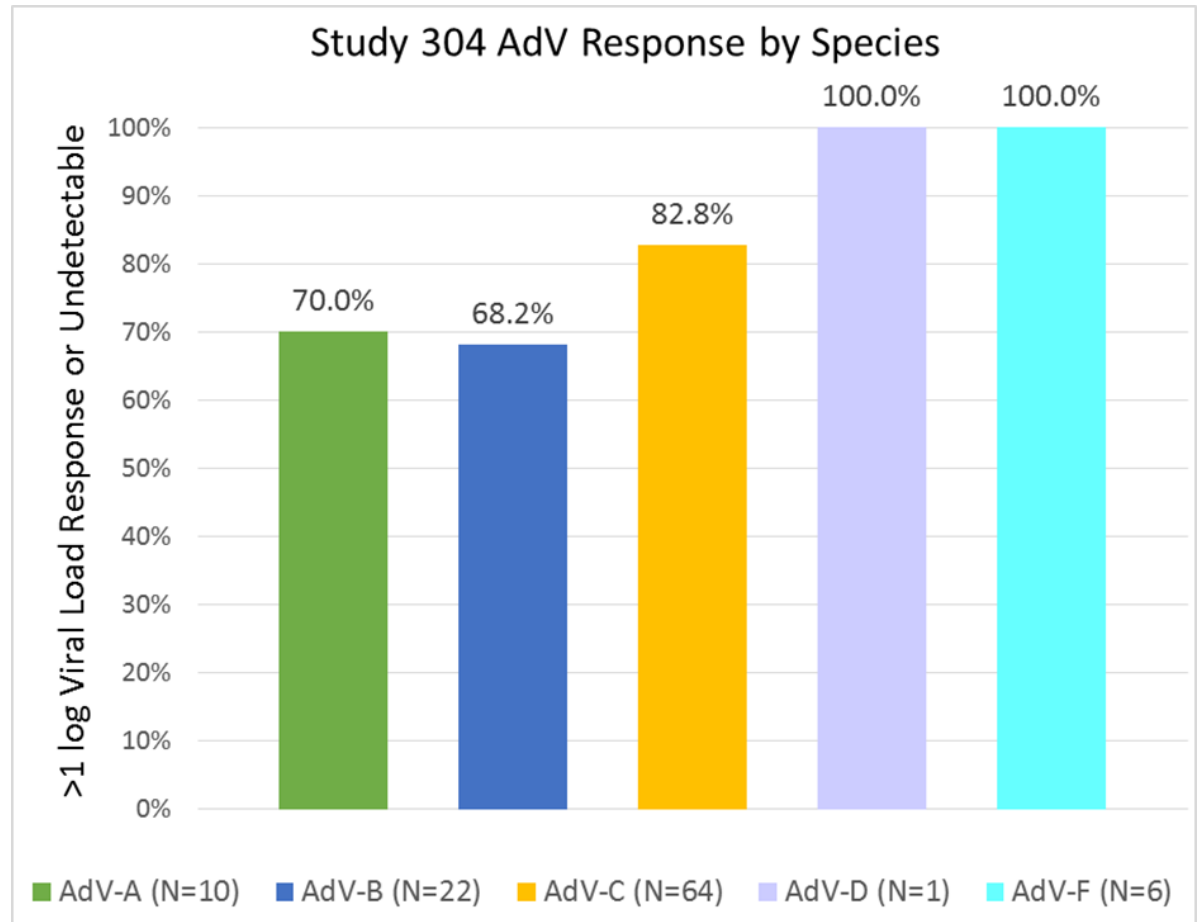
Among first 85 subjects enrolled in AdVise:

- 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 $\geq 3 \log_{10}$ 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 adverse event. The most common AEs were diarrhea, vomiting, abdominal pain, nausea, increased ALT, and acute GVHD.
- More than half of subjects enrolled had two or more dsDNA viral infections at study entry

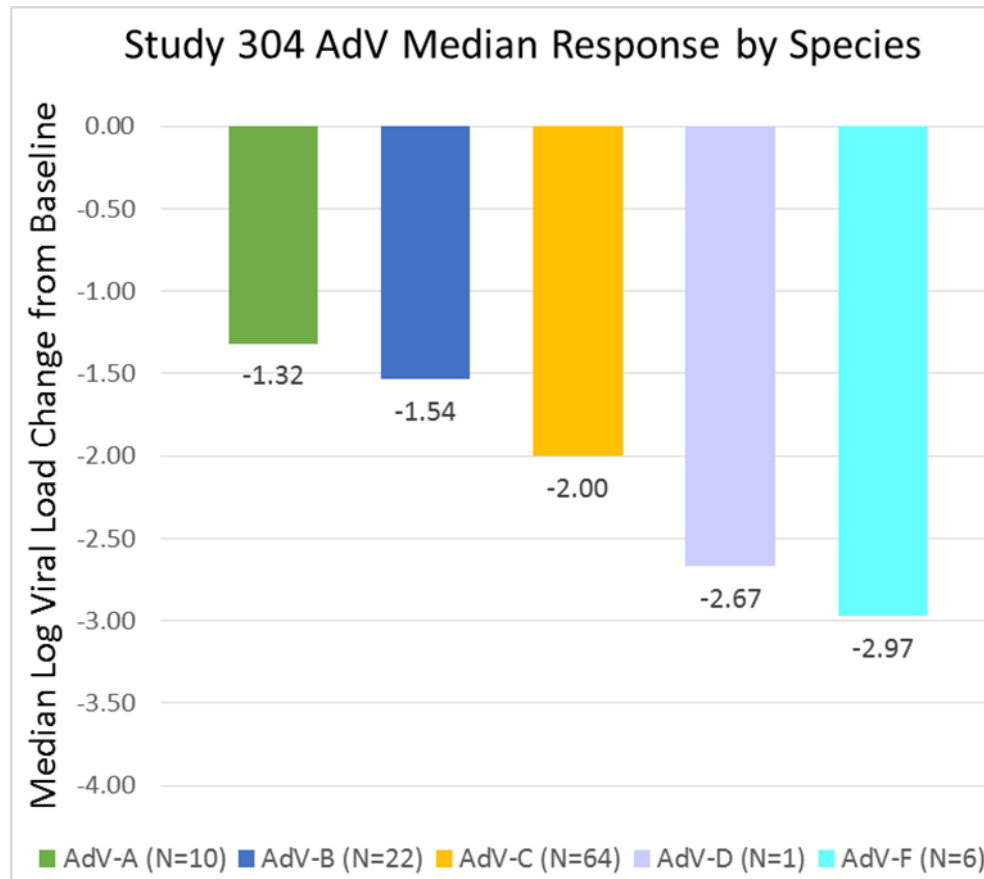
*Grimley, BMT Tandem Feb 2015

AdV Virologic Response by Species in AdVise Study (N=103 AdV Species in 98 Patients)

- The majority of patients had a 1 log drop or undetectable plasma AdV at the last timepoint on BCV
- Approximately half of patients had no detectable plasma AdV at the last timepoint on BCV:
 - 50% AdV-A (n=10)
 - 46% AdV-B (n=22)
 - 55% AdV-C (n=64)
 - 100% AdV-D (n=1)
 - 100% AdV-F (n=6)

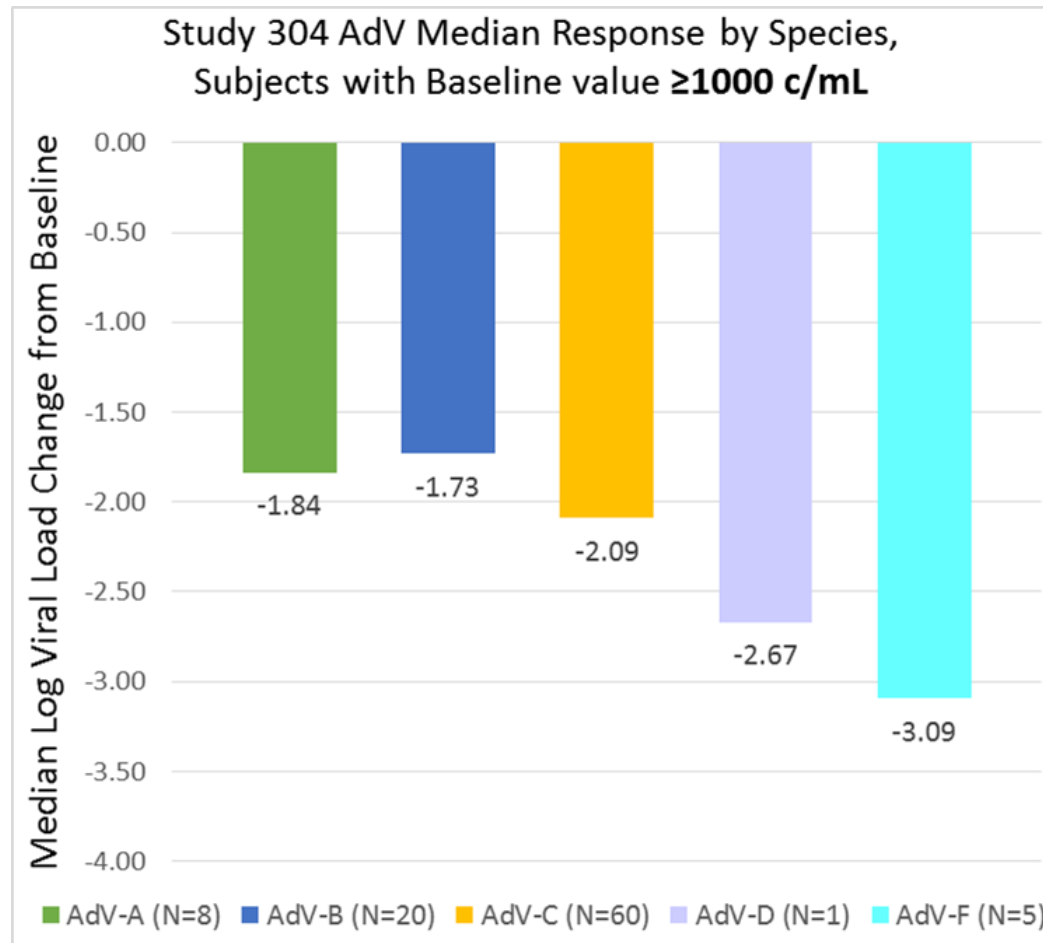


Virologic Response at Last Time on BCV therapy by AdV Species in AdVise (N=103 AdV Species in 98 Patients)



Patients with detectable baseline viremia and at least 2 weeks of treatment with BCV were assessed at the last timepoint on BCV therapy

Virologic Response at Last Time on BCV Therapy by AdV Species in AdVise with Baseline value ≥ 1000 c/ml



N=94 AdV species in 89 patients; 3 patients had 2 species and 1 had 3 species

BCV for Serious Adenovirus Infections: Summary

- Adenovirus infection can be life threatening in immunocompromised patients, especially in children undergoing allogeneic stem cell transplantation
 - BCV is in development to address this unmet clinical need
- Brincidofovir appears to have antiviral activity against all species and types of adenovirus that have been detected in clinical trials to date
- The AdVise trial analysis will compare survival and other outcomes to matched historical controls from the same medical centers

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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