TREATMENT OF ADENOVIRUS (AdV) INFECTION IN ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANT PATIENTS WITH BRINCIDOFOVIR: FINAL 36 WEEK RESULTS FROM THE ADVISE TRIAL

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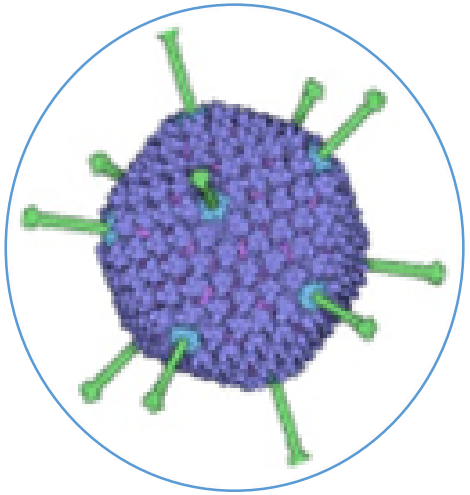
Adenovirus: An Important Cause of Mortality & Morbidity After Hematopoietic Cell Transplantation

- Significant infections
  - Gut, Liver, Respiratory, Urine, CNS
  - Particularly in children

- In untreated HCT recipients, mortality rates of up to 26% have been reported in patients with localized infection and 50-100% in patients with AdV pneumonia and disseminated disease[2]



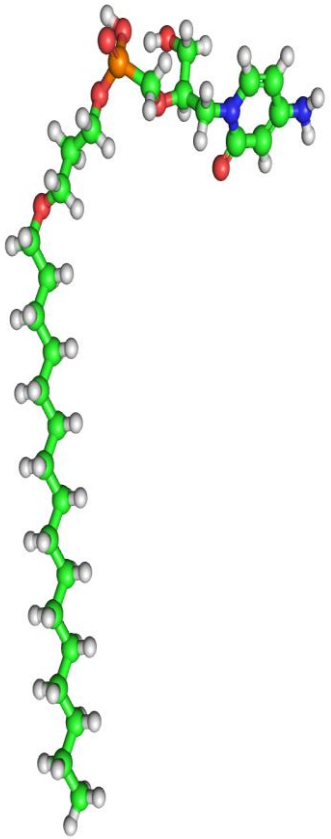
- Death generally occurs in the first 60 days after diagnosis[1–3]

- No approved treatment

1. Feghoul L, et al. *Clin Microbiol Infect* 2015;21:701–9. 2. Lion T. *Clin Microbiol Rev* 2014;27:441–62.
3. Mynarek M, et al. *Biol Blood Marrow Transplant* 2014;20:250–6.

Brincidofovir (BCV, CMX001)

- BCV is a broad-spectrum antiviral with high *in vitro* potency against all AdV subtypes[1]
- Intracellular cleavage of BCV allows cidofovir to be delivered directly to the site of viral replication
  - Increases antiviral potency
  - Low risk of nephrotoxicity or myelotoxicity[2-4]
- High barrier to viral resistance



1. Bae A, et al. Presented at BMT Tandem 2016.
2. Morrison M, et al. Presented at the World Transplant Congress, July 2014. 3. Grimley M, et al. Presented at the EBMT meeting, April 2013.
4. Tippin T, et al. Ther Drug Monit. 2016;38:777-86.

AdVise: Study Overview and Objectives

- Conducted between March 2014 and April 2016
- AdVise was an open-label, multicenter study to evaluate BCV treatment of AdV infection in pediatric and adult patients
  - BCV suspension or tablets were administered **orally** twice weekly (BIW) for 12 weeks (extensions permitted for ongoing or recurrent infection)
  - Dose: 100 mg BIW for ≥50 kg, 2 mg/kg BIW for <50 kg
- Enrolled subjects were assigned to one of three cohorts **based on baseline criteria**:
  - **Cohort A:** Allo-HCT recipients at risk of progression to disseminated AdV disease (either localized* AdV infection or asymptomatic viremia)
  - **Cohort B:** Allo-HCT recipients with disseminated** AdV disease
  - **Cohort C:** All other patients with serious AdV infections
- Final analysis of outcomes at 36 weeks post-first BCV dose in the 158 allo-HCT recipients (**Cohorts A & B**)
  - Includes ~24 weeks of off-treatment follow-up

* Probable or definitive symptomatic AdV disease in one of the organ systems with a positive or detectable AdV DNA measurement in the corresponding body fluid or compartment AND either an undetectable AdV viremia or two detectable AdV viremia measurements < 1,000 copies/mL, AND who does not have disseminated AdV disease as defined below.

** AdV positivity in two or more non-plasma body fluids or compartments and symptomatic in at least one of the organ systems or with fever (> 100.4°F) of unknown origin OR probable/definitive AdV disease in one of the organ systems with a positive or detectable AdV DNA measurement in the corresponding body fluid or compartment AND an AdV viremia ≥ 1,000 copies/mL.

AdVise: Study Overview and Objectives, cont.

- *Primary endpoint*:
  - All-cause mortality at Day 60 following initiation of BCV in allo-HCT recipients with disseminated AdV disease (Cohort B)
    - All subjects were followed until Week 36

- *Secondary endpoints*:
  - Incidence of all-cause mortality through Day 30, Day 90, Week 24, and Week 36 post-first BCV dose
  - Incidence of and time to undetectable AdV PCR at any time on treatment
  - Incidence of and time to undetectable AdV PCR at last on-treatment value

AdVise: Baseline Characteristics Show Important Differences Between Adults and Children in AdVise

		Cohort A (Localized or asymptomatic)		Cohort B (Disseminated)	
		Adult (N=23)	Pediatric (N=42)	Adult (N=35)	Pediatric (N=58)
Age, years	Median (range)	28 (18-68)	10 (1-17)	52 (18-69)	3 (0-16)
Race	White	17 (74)	32 (76)	28 (80)	42 (72)
Gender	Male	13 (57)	26 (62)	26 (74)	37 (64)
Prior CDV treatment within 30 days	Number (%)	9 (39)	21 (50)	8 (23)	32 (55)
Baseline Abs lymph count, cells/µL	Median (range)	615 (180–2060)	345 (0–1880)	230 (0–2470)	445 (0–2460)
Baseline CD4+ cell count, cells/µL	Median (range)	75 (2–543)	13 (0–313)	6 (0–240)	18 (0–319)
Acute GvHD	Any	10 (43)	14 (33)	13 (37)	13 (22)
	≥ Grade III	2 (9)	7 (17)	7 (20)	8 (14)

All values are n (%) unless otherwise stated. Cohort A had localized AdV infection or asymptomatic viremia. Cohort B had disseminated disease. AdV, adenovirus; CDV, cidofovir; SD, standard deviation, GvHD, graft-versus-host disease.

AdVise: Majority of patients received serotherapy or T cell depleted grafts

			Cohort A (Localized or asymptomatic)		Cohort B (Disseminated)	
			Adult (N=23)	Pediatric (N=42)	Adult (N=35)	Pediatric (N=58)
HCT Conditioning	n(%)	Myeloablative	17 (74)	30 (71)	19 (54)	31 (54)
		Reduced Intensity	5 (22)	12 (29)	12 (34)	25 (44)
		None	1 (4)	0	2 (6)	1 (2)
HCT Type*	n(%)	Cord	6 (26)	11 (26)	5 (14)	15 (26)
		Haploidentical BM/PBSC	2 (9)	5 (12)	6 (17)	8 (14)
		Matched Related BM/PBSC	5 (22)	7 (17)	7 (20)	8 (14)
		Matched Unrelated BM/PBSC	7 (30)	13 (31)	10 (29)	22 (39)
		Mismatched BM/PBSC	3 (13)	6 (14)	7 (20)	4 (7)
***Ex vivo* T-cell Depletion or CD34 Selection**	n(%)		10 (44)	8 (19)	15 (43)	10 (18)
ATG or alemtuzumab used	n(%)		14 (61)	31 (73)	26 (74)	39 (67)

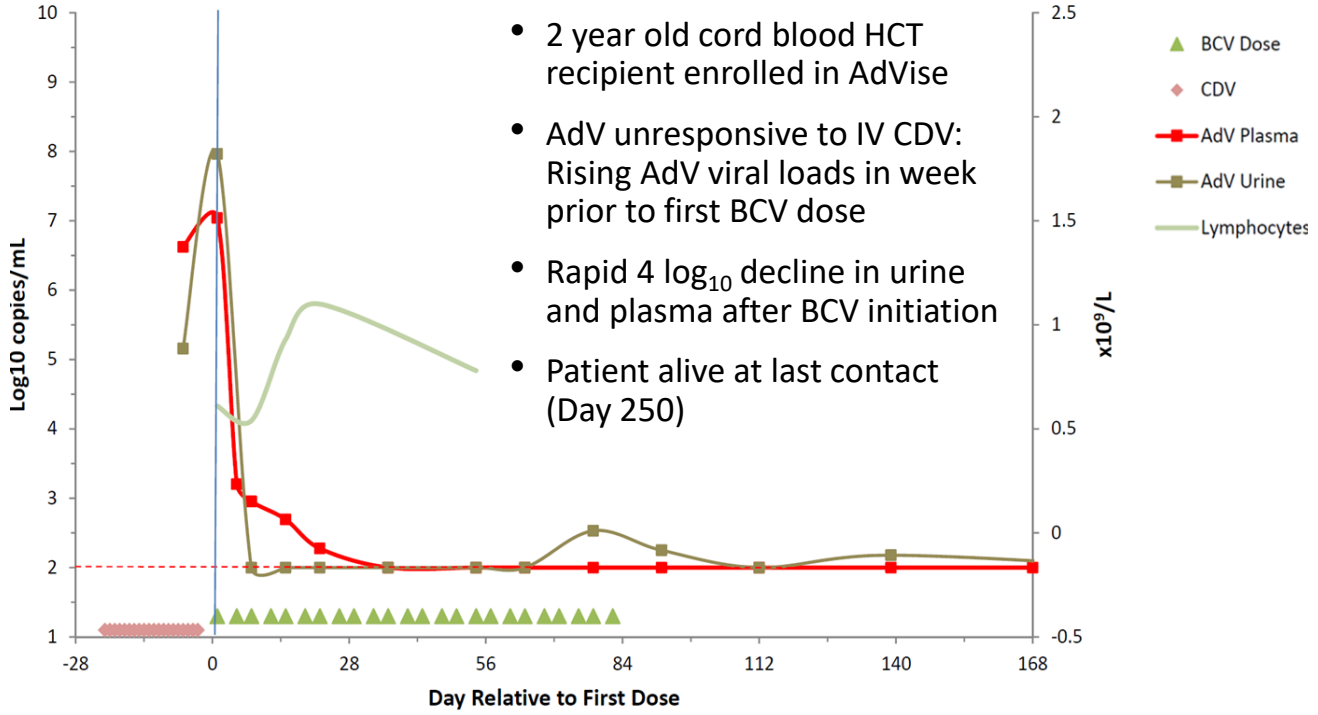
*One pediatric subject in cohort B did not receive HCT transplant at baseline, but already had a disseminated AdV disease during conditioning regimen.
Cohort A had localized AdV infection or asymptomatic viremia. Cohort B had disseminated disease.
ATG, anti-thymocyte globulin; HCT, hematopoietic cell transplant.

AdVise: Pediatric Patients Were Treated Longer Than Adults

		Cohort A (Localized or asymptomatic)		Cohort B (Disseminated)	
		Adult (N=23)	Pediatric (N=42)	Adult (N=35)	Pediatric (N=58)
Treatment duration, days	Mean (SD)	58.5 (50.2)	80.3 (56.8)	50.3 (40.5)	85.0 (58.0)
Number of BCV doses	Median (range)	9 (2–49)	22 (1–50)	10 (1–40)	23 (2–47)
Treatment course	Completed	4 (17)	20 (48)	7 (20)	32 (55)
	Did not complete	19 (83)	22 (52)	28 (80)	26 (45)
Reason for treatment discontinuation	Adverse event	6 (26)	9 (21)	8 (23)	4 (7)
	Death	4 (17)	6 (14)	11 (31)	12 (21)
	Other	9 (39)	7 (17)	9 (26)	10 (17)
Time from transplant to 1st dose, days	Median (range)	143 (54-504)	61 (7-443)	76 (1-2225)	57 (10-542)
Times from AdV diagnosis to 1st dose, days	Median (range)	17 (2-85)	12 (2-171)	10 (2-93)	12 (1-84)
AdV viremia at baseline, log10 c/mL	≥4 log10	6 (26)	7 (17)	27 (77)	32 (55)
	Median (range)	2.4 (2-6)	2.3 (2-6)	5.1 (2-8)	4.1 (2-9)

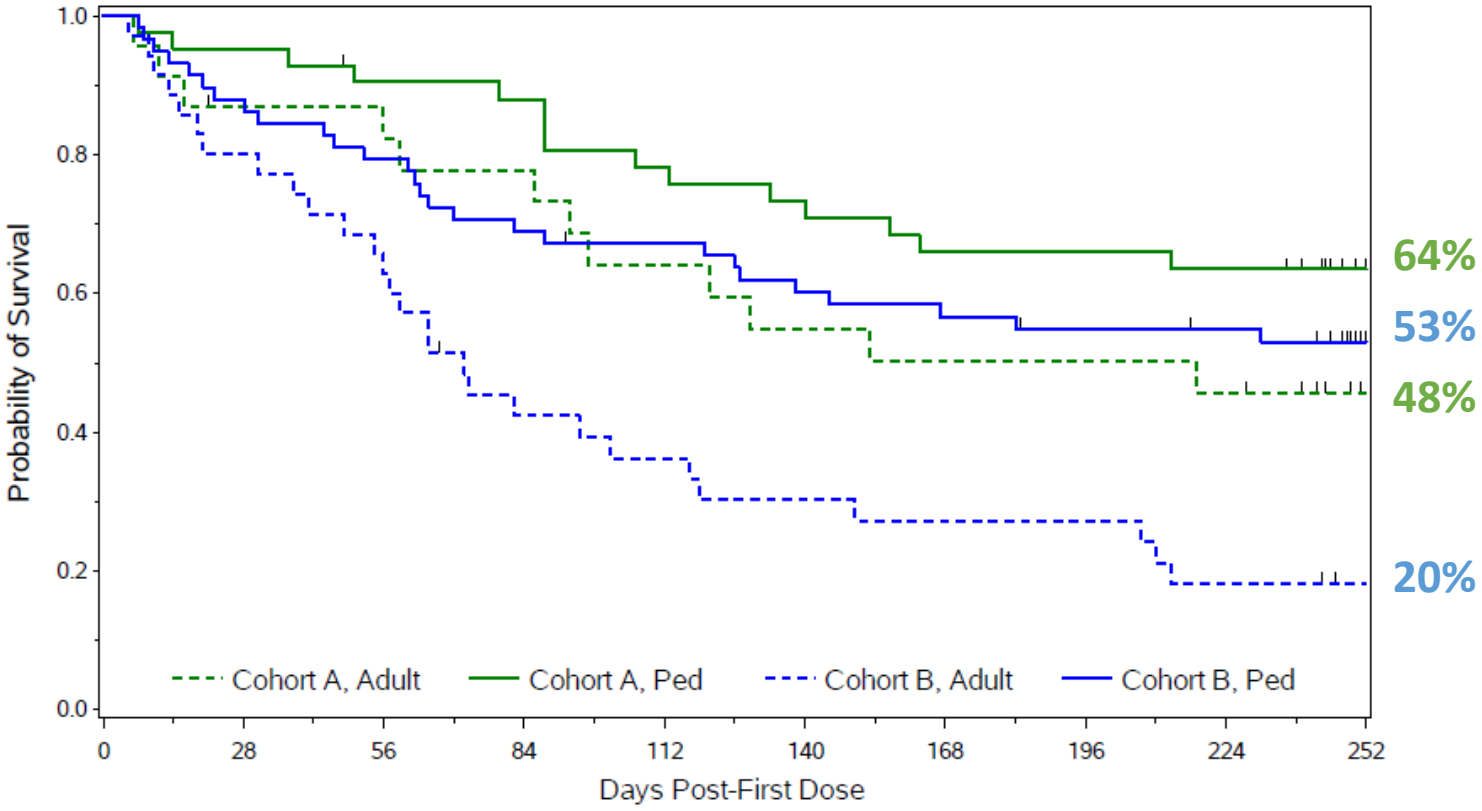
All values are n (%) unless otherwise stated. Cohort A had localized AdV infection or asymptomatic viremia. Cohort B had disseminated disease. BCV, brincidofovir; SD, standard deviation.

AdVise: A Representative Case of Robust Antiviral Response, Even after IV CDV Failure



- At Week 4, declines of ≥2 $\log_{10}$ c/mL or undetectable AdV viremia were seen in 76% of all pediatric patients, and in 45% of all adult patients
- In patients with baseline CD4 counts <50 cells/µL, 55% in Cohort A and 52% in Cohort B had ≥2 $\log_{10}$ c/mL decline or undetectable AdV at Week 4
- Median time to clear plasma was only 8 days in pediatric and adult patients with < 4log10 c/mL, vs. 26 days (pediatric) and 23 days (adults) with > 4log10 c/mL at Baseline

AdVise: All-Cause Mortality was Lower in Pediatric vs Adult Subjects and Cohort A vs B



- Cohort A: Adults (N=23) vs. Pediatrics (N=42): log-rank p=0.11, HR (95% CI) 1.8 (0.86, 3.8)
- Cohort B: Adults (N=35) vs. Pediatrics (N=58): log-rank p=0.0008, HR (95% CI) 2.4 (1.4, 4.1)

Cohort A had localized adenovirus infection or asymptomatic viremia. Cohort B had disseminated disease.

AdVise: AdV-related Mortality at Week 36 was Low with Earlier Treatment (Cohort A) and in Pediatric Disseminated Disease

	All-cause mortality		Non-relapse mortality		AdV-related mortality	
	Adult	Pediatric	Adult	Pediatric	Adult	Pediatric
Cohort A	**n=23**	**n=42**	**n=23**	**n=42**	**n=23**	**n=42**
Day 30	13%	5%	13%	2%	4%	0%
Day 60	22%	10%	17%	7%	4%	5%
Day 90	26%	19%	22%	14%	4%	5%
Week 24	48%	33%	44%	26%	4%	10%
Week 36	52%	36%	44%	26%	4%	10%
Cohort B	**n=35**	**n=58**	**n=35**	**n=58**	**n=35**	**n=58**
Day 30	20%	14%	17%	10%	11%	7%
Day 60	43%	21%	40%	14%	29%	7%
Day 90	57%	33%	54%	24%	40%	10%
Week 24	71%	43%	66%	35%	46%	14%
Week 36	80%	47%	66%	38%	46%	14%

- Lower AdV-related mortality in adults with localized vs. disseminated disease
  - May reflect different biology (early reactivation in peds vs. incident infection in adults)
  - Routine surveillance more common in peds – diagnosis later in disease course for adults

AdVise: Rapid Virologic Response was Associated with Improved Survival at Week 36 in Both Pediatric and Adult Subjects

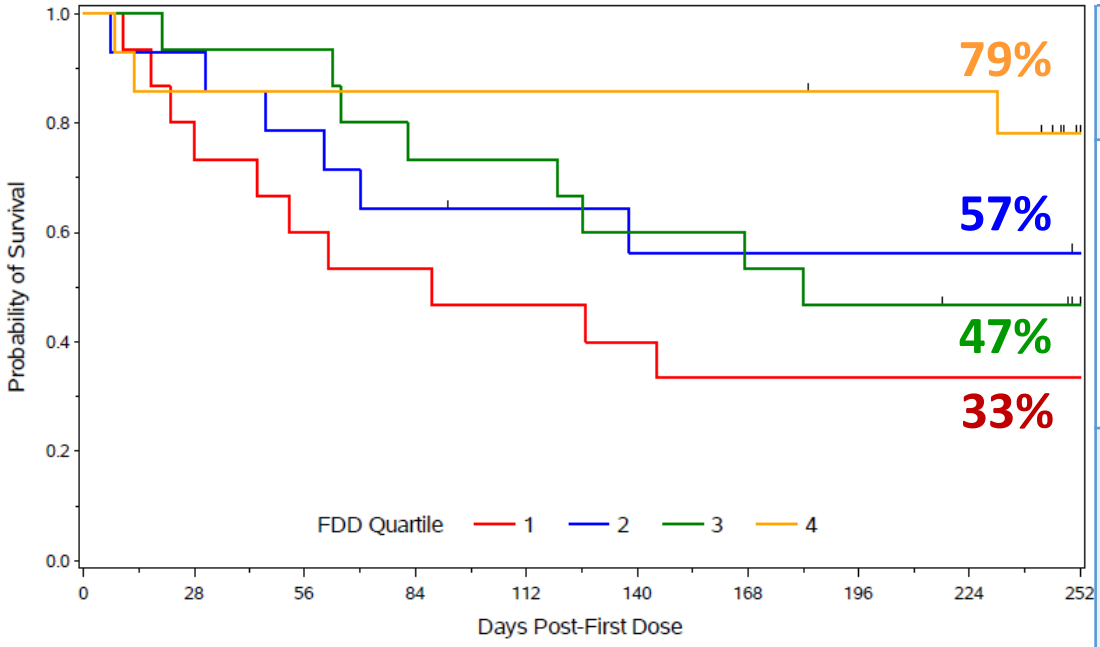
Definition of Responder	Pediatric (N=100)			Adults (N=58)		
	Proportion of Responders [a]	Mortality in Responders	Mortality in Non-responders	Proportion of Responders [a]	Mortality in Responders	Mortality in Non-responders
Cohort A (asymptomatic or localized infection; N=65)						
ND at wk 6	17/25 (68%)	5/17 (29%)	2/8 (25%)	8/13 (62%)	4/8 (50%)	4/5 (80%)
Cohort B (disseminated disease; N=93)						
ND at wk 6	28/41 (68%)	7/28 (25%)	7/13 (54%)	10/24 (42%)	5/10 (50%)	13/14 (93%)
		p=0.031[b]			p=0.0004[b]	
		Adv-Associated Mortality			**AdV-Associated Mortality**	
		1/28 (4%)	**2/13 (15%)**		**0/10 (0%)**	**10/14 (71%)**

All values are n/N (%).

A Cox model incorporating age group was used to compare mortality at 36 weeks in responders and non-responders. **Responders are defined as subjects who achieved undetectable viremia at Week 6**, with non-responders defined as subjects who did not achieve the specified cut-off. [a] Denominator: Subjects with baseline AdV viremia still on study at wk 6; [b] responders vs. non-responders, Cox model for time to death; all Cohort A comparisons not p<0.05; ND = no detectable viremia

AdVise: ~80% Survival in Pediatric Patients in the 4th Enrollment Quartile (Cohort B)

- Patients enrolled at initiation of trial had extensive prior cidofovir use, high AdV viral load, longest period from diagnosis to first BCV dose
- In the final quartile of enrollment, patients received brincidofovir more quickly after AdV diagnosis



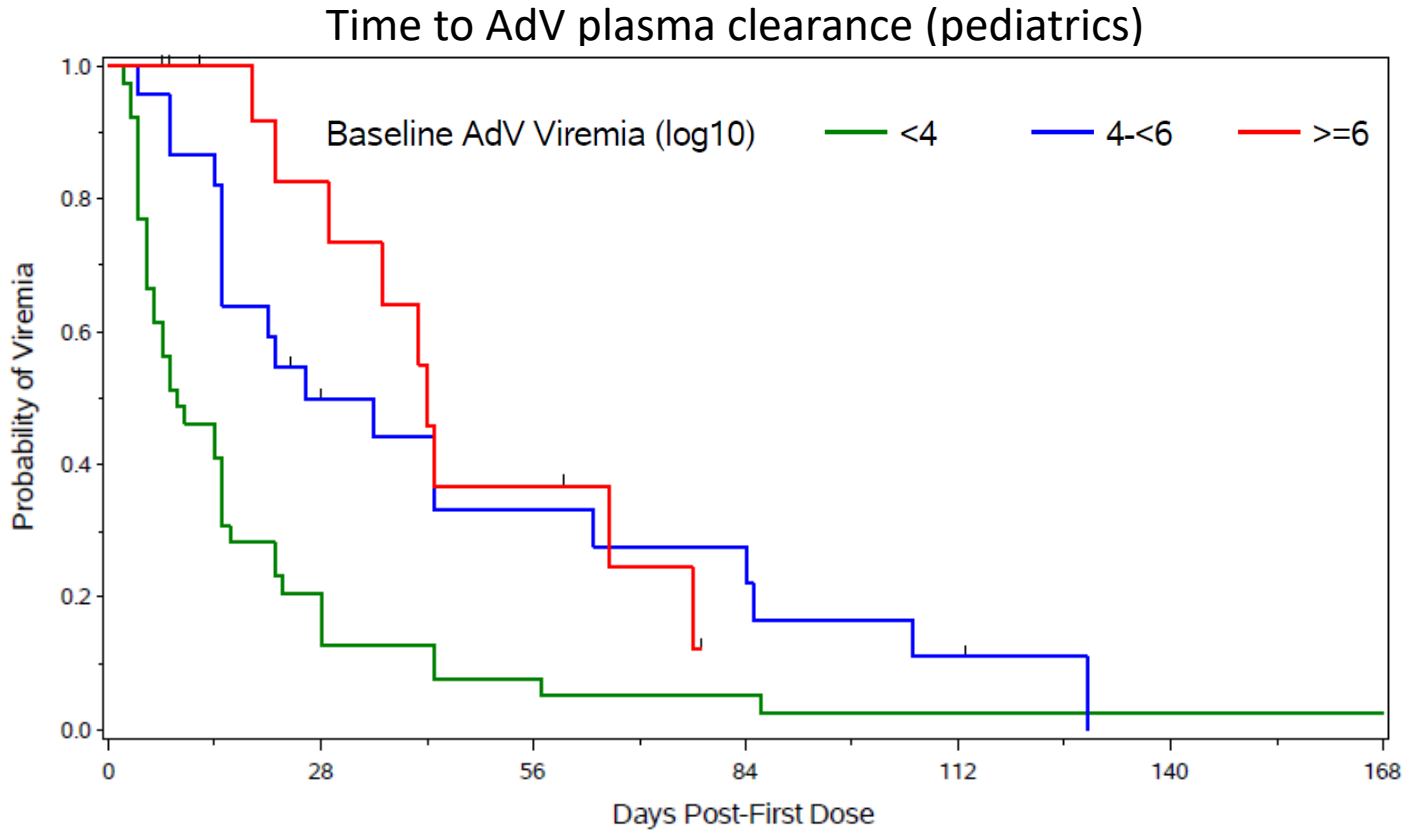
At Initiation of BCV	First Quartile (n=15)	Fourth Quartile (n=14)
>2 prior doses IV cidofovir	11 (73%)	2 (14%)
Days from AdV diagnosis (median, IQR)	22 (12, 44)	6.5 (4, 9)
AdV BL VL (median, IQR in log_{10} c/mL)	5.4 (3.1, 6.1)	3.6 (2.3, 5.8)

AdVise: Few TEAEs led to discontinuation, particularly in pediatrics

Treatment-Emergent Adverse Event (TEAE)		Cohort A (Localized or asymptomatic)		Cohort B (Disseminated)	
		Adult (N=23)	Pediatric (N=42)	Adult (N=35)	Pediatric (N=58)
Subjects with any TEAE		23 (100)	40 (95)	35 (100)	58 (100)
Gastrointestinal		16 (70)	34 (81)	30 (86)	43 (74)
	Abdominal pain	9 (39)	8 (19)	10 (29)	10 (17)
	Diarrhea	10 (44)	18 (43)	12 (34)	25 (43)
	Nausea	6 (26)	3 (7)	10 (29)	5 (9)
	Vomiting	8 (35)	9 (21)	7 (20)	10 (17)
Laboratory tests		13 (57)	29 (69)	22 (63)	38 (66)
	Alanine aminotransferase increased	1 (4)	10 (24)	4 (11)	11 (19)
	Aspartate aminotransferase increased	1 (4)	8 (19)	5 (14)	10 (17)
	Blood bilirubin increased	1 (4)	8 (19)	4 (11)	12 (21)
Immune system	Acute graft versus host disease	5 (22)	17 (41)	16 (46)	23 (40)
Subjects with any TEAE leading to study drug discontinuation		6 (26)	14 (33)	11 (31)	8 (14)

All values are n (%).
Cohort A had localized adenovirus infection or asymptomatic viremia. Cohort B had disseminated disease.
AE, adverse event; TEAE, treatment-emergent adverse event.

AdVise: Time to clear plasma was shorter than time to GI events in pediatric patients (Cohort A and B)



- Median time to clear plasma was only 8 days in pediatric patients with < 4log10 c/mL
- 72% of pediatric subjects with Baseline plasma <5 $\log_{10}$ cleared plasma within 4 weeks
- Median time to grade 2 diarrhea or new onset GI GVHD: 28 days

AdVise: Conclusions

- BCV showed clear antiviral activity
- All-cause and AdV-associated mortality were lower in pediatric patients than in adult patients
  - Pediatric patients had onset of AdV earlier after HCT, and had lower baseline viral loads
  - Likely in part due to prospective screening for AdV in pediatric allo-HCT
- Rapid declines in AdV viral load were observed with BCV, even in HCT recipients without immune reconstitution
  - Median time to AdV clearance from plasma was only 1-3 weeks and correlated with BL plasma load, suggesting that prompt initiation after AdV detection and shorter courses of therapy may be effective
  - In patients with disseminated disease, viral clearance from plasma at six weeks was associated with better overall survival
- Lower mortality in pediatric patients enrolled later (2015) in the study
  - Early use of BCV appears to drive improved outcomes
  - BCV tolerability appeared to be improved in pediatric patients
- Together, these data suggest that further study of short course BCV in pediatric HCT recipients with adenovirus infection is warranted

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- Children’s Hospital New Orleans
- The Children’s Hospital of Philadelphia
- Stanford University
- Children's Hospital Colorado
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