Treatment of Adenovirus (AdV) Infection in Allogeneic Hematopoietic Cell Transplant (HCT) Patients (pts) with Brincidofovir: 24 Week Interim Results from the AdVise Trial

2339

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INTRODUCTION

- AdV infection is an important cause of morbidity and mortality following HCT. 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. Death generally occurs in the first 60 days after diagnosis.[1-3]
- There is no approved treatment for AdV infection or disease, although intravenous (IV) gamma globulins and a reduction in immune suppression may be used, with or without off-label use of IV cidofovir (CDV).[4,5] However, CDV is associated with significant dose-limiting nephrotoxicity in up to 50% of patients[5] and myelotoxicity, which can be a direct threat to the new hematopoietic graft.
- Brincidofovir (BCV) is an orally administered lipid conjugate of CDV with high *in vitro* potency against all AdV subtypes.
- Cleavage of BCV to release CDV occurs intracellularly, limiting the concentration of CDV in the plasma.
- BCV is not associated with nephrotoxicity or myelotoxicity.[6,9]
- BCV has shown promise as a preemptive treatment in allogeneic HCT (allo HCT) patients with asymptomatic AdV viremia in a Phase 2 study and as a treatment in serious AdV infection or disease under compassionate use regulations.[10-13]

Aims

- CMX001-304 (AdVise Trial; ClinicalTrials.gov ID: NCT02087306) was an open-label, multicenter study to evaluate the efficacy, safety, and overall tolerability of BCV for the treatment of AdV infection in pediatric and adult patients.
  - The primary efficacy endpoint for the study was the incidence of all-cause mortality at Day 60 post-first BCV dose in allo HCT patients enrolled with disseminated AdV disease.
- An interim analysis of outcomes at 24 weeks post-first BCV dose (at least 12 weeks of off-treatment follow-up) in the 158 allo HCT recipients who received BCV for AdV infection is presented here.

METHODS

Study CMX001-304

Inclusion criteria

- Patients (aged ≥2 months) who had undergone HCT, solid organ transplant or had another underlying immunodeficiency, with disseminated AdV disease or at risk of progression to disseminated disease, and patients with unknown immune status who presented with disseminated AdV disease.
- Three cohorts were defined:
  - **Cohort A:** Allo HCT recipients at risk of progression to disseminated AdV disease (i.e., either localized AdV infection or asymptomatic viremia).
  - **Cohort B:** Allo HCT recipients with disseminated AdV disease.
  - **Cohort C:** All other immunocompromised patients regardless of disease status, as well as patients with unknown immune status who presented with disseminated AdV disease.
- HCT recipients in Cohorts A and B were included in this interim analysis, with additional sub-group analysis of adult and pediatric (i.e., <18 years of age) patients within each cohort.

Study treatment and procedures

- All patients received open-label BCV twice weekly (BIW) for 12 weeks (Day 1 through Week 12), extendable for up to 12 additional weeks (through Week 24) in patients with ongoing infection or at high risk for recurrence of AdV infection.
  - After completing treatment, all patients were followed until Week 36.
  - Up to 12 weeks BCV (to maximum 24 weeks cumulative treatment) was available for rescue therapy to treat AdV recurrence during the post-treatment follow-up period.
- Patients weighing ≥50 kg received BCV 100 mg BIW; patients weighing <50 kg received weight-based doses of 2 mg/kg (not-to-exceed 100 mg) BIW.
- Concurrent use of IV CDV, leflunomide, vidarabine, systemic ribavirin, anti-AdV vaccines, and cell-based therapies was prohibited.
- Plasma for analysis of AdV DNA viremia was collected at screening, pre-dose on Day 1 (baseline), Day 4, weekly throughout the treatment phase, and at post-treatment follow-up visits on Weeks 13, 14, 16, 18, 20, 22, 24, 26, 32, and 36.
  - AdV DNA viremia was measured by quantitative polymerase chain reaction (AdV 7500 qPCR, Viracor-IBT Laboratories, Lee's Summit, MO, USA) with a lower limit of detection of 100 c/mL and lower limit of quantification (LLOQ) of 190 c/mL.
- All patients were monitored for adverse events (AEs) and underwent regular safety monitoring, including routine clinical laboratory safety assessments, assessment of renal function, targeted physical examination, and vital signs measurements, throughout the treatment and post-treatment phases.

RESULTS

Demographics

- A total of 100 pediatric and 58 adult allo HCT patients were enrolled in the study and assigned to Cohort A (43 pediatric and 23 adult patients) or B (57 pediatric and 35 adult patients).
- Patient demographics and other baseline characteristics are shown in **Table 1**, with details of the patients' stem cell transplants summarized in **Table 2**.
  - Prior IV CDV use was 44% overall and ranged from 23% to 56% by cohort and age group.
  - Adult patients were enrolled at a later time post-transplant than pediatric patients, although the time from diagnosis of AdV infection to first BCV dose was similar in both age groups.
  - Baseline AdV viremia was detected in 65% of patients in Cohort A and 92% in Cohort B, with AdV viremia ≥4 $\log_{10}$ c/mL observed in 21% and 63% of patients in Cohorts A and B, respectively.

Table 1. Baseline Characteristics

		Cohort A		Cohort B	
		Adult (N=23)	Pediatric (N=43)	Adult (N=35)	Pediatric (N=57)
Age, years	Mean (SD)	36.3 (18.2)	9.1 (4.8)	46.1 (17.8)	4.7 (4.4)
Race	White	17 (74)	32 (74)	27 (77)	38 (67)
Sex	Male	13 (57)	26 (60)	26 (74)	37 (65)
Baseline weight, kg	Mean (SD)	68.6 (15.2)	34.6 (17.2)	73.9 (17.8)	20.7 (13.8)
Prior CDV treatment		9 (39)	21 (49)	8 (23)	32 (56)
ALC count, cells/µL	Median (range)	615 (180–2060)	340 (0–1880)	230 (0–2470)	470 (0–2460)
CD4+ cell count, cells/µL	Median (range)	75 (2–543)	17 (0–313)	6 (0–240)	16 (0–319)
Time from transplant, days	Mean (SD)	164.8 (112.5)	89.3 (93.9)	146.5 (366.5)	92.0 (109.6)
Time from AdV diagnosis, days	Mean (SD)	22.7 (21.8)	19.7 (26.9)	16.9 (20.0)	21.2 (24.6)
AdV viremia at baseline	Not detected	7 (30)	16 (37)	1 (3)	6 (11)
	Mean (SD), $\log_{10}$ c/mL	3.3 (1.5)	2.8 (1.2)	5.2 (1.5)	4.6 (2.0)
	≥4 $\log_{10}$ c/mL	6 (26)	8 (19)	27 (77)	31 (54)
BKV viruria	+	15 (65)	28 (65)	20 (57)	19 (33)
	–	6 (26)	13 (30)	13 (37)	30 (53)
CMV viremia	+	9 (39)	10 (23)	10 (29)	14 (25)
	–	13 (57)	32 (74)	25 (71)	39 (68)
Acute GvHD	Any	5 (22)	11 (26)	12 (34)	11 (19)
	Grade ≥III	2 (9)	7 (16)	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; ALC, absolute lymphocyte count; BKV, BK virus; CDV, cidofovir; CMV, cytomegalovirus; GvHD, graft-versus-host disease; SD, standard deviation.

Table 2. Transplant Details

		Cohort A		Cohort B	
		Adult (N=23)	Pediatric (N=43)	Adult (N=35)	Pediatric (N=57)
HCT conditioning	Myeloablative	17 (74)	30 (70)	19 (54)	32 (56)
	Reduced intensity	5 (22)	13 (30)	12 (34)	24 (42)
	None	1 (4)	0	2 (6)	1 (2)
HCT source*	Bone marrow	4 (17)	21 (49)	3 (9)	25 (44)
	Cord	6 (26)	11 (26)	5 (14)	16 (28)
	Peripheral blood stem cells	12 (52)	11 (26)	27 (77)	16 (28)
HCT type	Cord	6 (26)	11 (26)	5 (14)	16 (28)
	Haploidentical	2 (9)	5 (12)	6 (17)	8 (14)
	Matched related	5 (22)	7 (16)	7 (20)	8 (14)
	Matched unrelated	7 (30)	14 (33)	10 (29)	21 (37)
	Mismatched related	0	0	3 (9)	0
	Mismatched unrelated	3 (13)	6 (14)	4 (11)	4 (7)
***Ex vivo* T-cell depletion**	Y	9 (39)	5 (12)	15 (43)	5 (9)
ATG or Campath[6]	Y	14 (61)	31 (73)	28 (80)	38 (67)

All values are n (%) unless otherwise stated.
Cohort A had localized AdV infection or asymptomatic viremia. Cohort B had disseminated disease.
*Excludes 1 adult patient in Cohort A who received a mismatched, unrelated HCT, with no other details provided.
AdV, adenovirus; ATG, anti-thymocyte globulin; HCT, hematopoietic cell transplant.

Patient disposition and BCV exposure

- The median (range) duration of treatment with BCV (not accounting for breaks in treatment, but including any break between completing the treatment period and initiating rescue therapy) was 81 days (1–271) in pediatric patients and 47 days (1–170) in adult patients.
- The most common reasons for early treatment discontinuation were death or AEs (**Table 3**).

Table 3. BCV Exposure and Patient Disposition

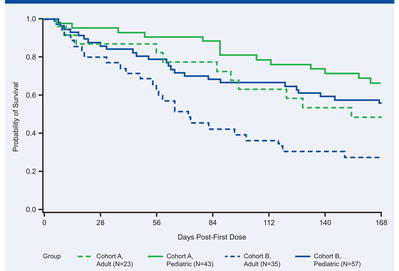
		Cohort A		Cohort B	
		Adult (N=23)	Pediatric (N=43)	Adult (N=35)	Pediatric (N=57)
Treatment duration, days	Mean (SD)	58.5 (50.2)	81.3 (57.5)	47.4 (36.8)	83.4 (57.5)
Number of BCV doses	Median (range)	9 (2–49)	23 (1–50)	10 (1–40)	22 (2–47)
Treatment status	Completed	4 (17)	21 (49)	8 (23)	28 (49)
	Did not complete	19 (83)	22 (51)	27 (77)	29 (51)
Reason for treatment discontinuation	Adverse event	7 (30)	7 (16)	8 (23)	5 (9)
	Death	5 (22)	6 (14)	9 (26)	13 (23)
	Other	7 (30)	9 (21)	10 (29)	11 (19)
Study status	Completed	6 (26)	18 (42)	3 (9)	17 (30)
	Ongoing	2 (9)	11 (26)	7 (20)	12 (21)
	Did not complete	15 (65)	14 (33)	25 (71)	28 (49)
Reason for study discontinuation	Death	10 (43)	12 (28)	24 (69)	25 (44)
	Lost to follow-up	–	1 (2)	–	1 (2)
	Withdrew consent	3 (13)	1 (2)	1 (3)	2 (4)
	Other	2 (9)	5 (12)	5 (14)	5 (9)

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

Efficacy and virology

- The primary efficacy endpoint, all-cause mortality in Cohort B at Day 60, was 28%.
  - Any prior treatment with CDV in Cohort B appeared to have little impact on overall mortality (30% in patients with prior CDV use at Day 60 vs 27% in patients with no prior use of CDV).
- All-cause mortality was lower in pediatric patients than adult patients in both cohorts, and lower in Cohort A compared with Cohort B through Week 24 (**Figure 1** and **Table 4**).
- AdV-related mortality at Week 24 in pediatric patients was 9% in Cohort A and 14% in Cohort B (**Table 4**).
- Marked declines in AdV viremia were observed in both cohorts. A last on-treatment value of undetectable viremia was achieved in 61% of patients in Cohort A, and 49% of patients in Cohort B (**Table 5**).
  - At Week 4, declines of ≥2 $\log_{10}$ c/mL or undetectable levels of AdV viremia were seen in 76% of all pediatric patients, and in 44% of all adult patients.
    - A robust antiviral response was observed despite very low baseline lymphocyte counts and CD4 cell counts in this population. 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 levels of AdV at Week 4.

Figure 1. Kaplan–Meier Probability of Survival by Cohort and Age Group



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

Table 4. Mortality to Week 24

	All-cause mortality		Non-relapse mortality		AdV-related mortality	
	Adult	Pediatric	Adult	Pediatric	Adult	Pediatric
Cohort A	**N=23**	**N=43**	**N=23**	**N=43**	**N=23**	**N=43**
Day 30	13%	5%	13%	2%	4%	0
Day 60	22%	9%	17%	7%	4%	5%
Day 90	26%	19%	22%	14%	4%	5%
Week 24	48%	33%	44%	26%	4%	9%
Cohort B	**N=35**	**N=57**	**N=35**	**N=57**	**N=35**	**N=57**
Day 30	20%	14%	17%	11%	11%	7%
Day 60*	43%	19%	40%	14%	29%	7%
Day 90	57%	32%	54%	25%	40%	11%
Week 24	71%	42%	66%	35%	46%	14%

*Primary endpoint per protocol was the incidence of all-cause mortality at Day 60 post-first BCV dose in allo HCT patients with disseminated AdV disease (Cohort B). Assessments were not mutually exclusive; the endpoint adjudication committee was allowed to select more than one contributing factor for each event, with relapse-associated mortality assigned priority in the analysis.
AdV, adenovirus; allo HCT, allogeneic hematopoietic cell transplant; BCV, brincidofovir.

Table 5. Virologic Outcomes in Patients with AdV Viremia at Baseline

	Cohort A		Cohort B	
	Adult (N=14)	Pediatric (N=27)	Adult (N=34)	Pediatric (N=51)
≥2-$\log_{10}$ c/mL decline or undetectable AdV viremia at Week 4	6 (43)	22 (81)	15 (44)	37 (73)
Undetectable AdV viremia at any time	7 (50)	23 (85)	13 (38)	39 (76)
Undetectable AdV viremia at last on-treatment value	6 (43)	19 (70)	10 (29)	32 (63)
Median (range) time to undetectable AdV viremia (days)	43 (8, NE)	14 (5, 23)	NE (29, NE)	22 (15, 36)

All values are n (%) unless otherwise stated. Cohort A had localized AdV infection or asymptomatic viremia. Cohort B had disseminated disease.
LLOQ was 190 c/mL.
AdV, adenovirus; LLOQ, lower limit of quantification; NE, non-estimable.

Post hoc *analysis: Virologic response and mortality*

- A landmark analysis to investigate the correlation between rapid virologic response to treatment and time to subsequent mortality was performed using a Cox model to compare patients who achieved a decrease of ≥2 $\log_{10}$ c/mL or undetectable AdV viremia at Week 4, or undetectable AdV viremia at Week 6 (responders) with patients who did not (non-responders).
- In patients with disseminated AdV disease who were alive at Week 4, 84% of pediatric and 50% of adult patients were responders (i.e., had a decline of ≥2 $\log_{10}$ c/mL or undetectable plasma AdV, **Table 6**).
  - Response to treatment at Week 4 was associated with improved survival at Week 24 in both pediatric and adult patients; 75% of pediatric and 54% of adult responders survived to Week 24, compared with 29% and 15% of non-responders, respectively (hazard ratio 3.6, 95% confidence interval [CI] 1.7–7.7, p=0.001 in a Cox model including age group).
- In patients with disseminated AdV disease who were alive at Week 6, 68% of pediatric and 42% of adult patients were responders (i.e., had undetectable plasma AdV, **Table 6**).
  - Response to treatment at Week 6 was associated with improved survival at Week 24 in both pediatric and adult patients; 82% of pediatric and 70% of adult responders survived to Week 24, compared with 46% and 14% of non-responders, respectively (hazard ratio 6.2, 95% CI 2.6–14.6, p<0.0001 in a Cox model including age group).

Table 6. *Post hoc* analysis: Mortality at Week 24 in Responders and Non-Responders with Disseminated AdV Disease (Cohort B)

Responder definition	Adult patients			Pediatric patients		
	Proportion of responders	Mortality in responders	Mortality in non-responders	Proportion of responders	Mortality in responders	Mortality in non-responders
Week 4: ≥2 $\log_{10}$ c/mL or undetectable AdV viremia	13/26 (50)	6/13 (46)	11/13 (85)	36/43 (84)	9/36 (25)	5/7 (71)
		p=0.03			p=0.01	
Week 6: Undetectable AdV viremia	10/24 (42)	3/10 (30)	12/14 (86)	28/41 (68)	5/28 (18)	7/13 (54)
		p=0.001			p=0.01	

All values are n (%) unless otherwise stated. Responders were defined as patients who achieved a decrease of ≥2 $\log_{10}$ c/mL or undetectable AdV viremia at Week 4, or undetectable viremia at Week 6, with non-responders defined as patients who did not achieve the cut-off. A Cox model incorporating age group was used to compare mortality at 24 weeks in responders and non-responders.
AdV, adenovirus.

Safety

- A summary of AEs is shown in **Table 7**.
- Gastrointestinal (GI) symptoms, increases in serum transaminases and bilirubin, and acute graft-versus-host disease (GvHD) were the most commonly reported treatment-emergent AEs.
- There were no events reported that were suggestive of drug-related nephrotoxicity or myelosuppression.
- BCV was discontinued due to AEs in 20% of pediatric patients and 29% of adult patients, with GI events cited as the most common reason (5% and 14%, respectively).
- The most commonly reported fatal AEs in Cohort B were multiorgan failure (18% pediatric, 14% adults), acute GvHD (4% pediatric, 20% adults), AdV infection (4% pediatric, 14% adults), and respiratory failure (7% pediatric, 9% adults).

Table 7. Summary of AEs

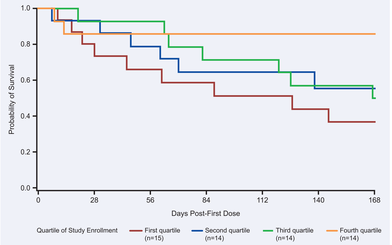
	Cohort A		Cohort B	
	Adult (N=23)	Pediatric (N=43)	Adult (N=35)	Pediatric (N=57)
Patients with any TEAE	23 (100)	41 (95)	35 (100)	57 (100)
Any gastrointestinal TEAE	16 (70)	35 (81)	29 (83)	42 (74)
Abdominal pain	9 (39)	8 (19)	9 (26)	11 (19)
Diarrhea	10 (43)	19 (44)	12 (34)	24 (42)
Nausea	6 (26)	1 (2)	10 (29)	6 (11)
Vomiting	8 (35)	9 (21)	7 (20)	10 (18)
Investigations	13 (57)	31 (72)	22 (63)	37 (65)
Alanine aminotransferase increased	1 (4)	10 (23)	4 (11)	11 (19)
Aspartate aminotransferase increased	1 (4)	8 (19)	5 (14)	10 (18)
Blood bilirubin increased	1 (4)	8 (19)	4 (11)	12 (21)
Any immune system TEAE	9 (39)	20 (47)	19 (54)	24 (42)
Acute graft-versus-host disease	5 (22)	16 (37)	15 (43)	23 (40)
Patients with any AE leading to study drug discontinuation	6 (26)	12 (28)	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.

Post hoc *analysis by enrollment quartile*

- The first patient(s) at each participating site may have experienced delays between diagnosis and treatment with BCV primarily because of the time required to secure institutional review board approval.
- A *post hoc* analysis of all-cause mortality through Week 24 by quartile of enrollment was conducted in patients with disseminated AdV disease to investigate potential changes in outcomes over the course of the study.
- Mortality was highest in pediatric patients enrolled in the first quartile of the study (60%), and lowest in pediatric patients enrolled in the last quartile (14%) (**Figure 2**); differences were less pronounced in adults (data not shown).

Figure 2. Kaplan–Meier Probability of Survival in Pediatric HCT Recipients with Disseminated Adenovirus Disease by Quartile of Study Enrollment



HCT, hematopoietic cell transplant.

CONCLUSIONS

- **All-cause and AdV-associated mortality were lower in pediatric patients than in adult patients.**
- **Marked declines in AdV viral load were observed with BCV, even in HCT recipients with low CD4 counts at baseline.**
  - **In patients with disseminated disease, early virologic response at 4 or 6 weeks was associated with better overall survival.**
  - **These findings confirm the observations made in patients who were treated for serious AdV infection through emergency investigational new drug and expanded access regulations in the US, where reduced AdV viral load in BCV recipients led to reductions in AdV-related symptoms and associated mortality.[10-13]**
- **Assessment of enrollment period as a covariate demonstrated a period effect, with lower mortality in Cohort B pediatric patients enrolled in the last quartile compared with those enrolled at the beginning of the study; differences were less pronounced in adults (data not shown).**
- **BCV was better tolerated in pediatric patients than in adults. The nature and frequency of AEs observed in this study were consistent with the known safety profile of BCV, with no new safety concerns identified.**
- **These data support the continued development of BCV as a potential therapeutic for AdV.**

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DISCLOSURES

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