CMX001, a Novel Broad Spectrum Antiviral, May Mitigate Signs of BK Virus (BKV) Associated Bladder and Kidney End-Organ Damage

Mommeja-Marin H.[1], Marty F.[2,3], Boeckh M.[4], Winston D.[5], Rowley S.D.[6], Godkin S.[1], Margolskee D.[1]

[1]Chimerix, Inc., Durham, USA, [2]Brigham and Women's Hospital, Boston, USA, [3]Dana Farber Cancer Institute, Boston, USA, [4]Fred Hutchinson Cancer Research Center, Seattle, USA, [5]UCLA Center for the Health Sciences, Los Angeles, USA, [6]Hackensack University Medical, Hackensack, USA

ICTS July 2012
MON.PO10.034

Introduction

BK virus (BKV) is a polyomavirus; a small, non-enveloped, double-stranded DNA (dsDNA) virus which was first isolated in 1971 from a renal transplant patient (initials BK) with ureteric stenosis.[1] Primary BKV infection normally occurs early in life, presenting as a mild disease with flu-like symptoms. Following primary infection, the virus establishes lifelong latency in urogenital epithelial cells, rarely causing disease in healthy adults. Conversely, BKV causes significant disease in patients with prolonged immunosuppression, such as BKV associated nephropathy (BKVAN) in renal transplant patients and hemorrhagic cystitis (HC) in hematopoietic stem cell transplant (HSCT) recipients.[2-5]

BKV infection is associated with HC in approximately 30% (5 to 60%) of HSCT recipients; the risk of HC is increased after myeloablative conditioning or mismatched donor HSCT. Although rarely fatal, HC episodes can be severe; very painful; associated with significant hematuria and clotting; may prolong hospitalization; and can result in impairment of kidney and/or bladder function.[5-6]

CMX001 is a novel, orally bioavailable broad spectrum lipid acyclic nucleoside phosphonate that is converted intracellularly into the active antiviral cidofovir diphosphate (CDV-PP), which has a long intracellular half-life of ~6.5 days.

CMX001 has broad spectrum in vitro antiviral activity against all dsDNA viruses of importance to immunocompromised patients, including transplant recipients, and has not been associated with either myelosuppression or nephrotoxicity in extensive clinical trials. For comparison with CMX001, the in vitro antiviral activity of relevant, nucleoside/nucleotide analogs against cytomegalovirus (CMV), BKV, adenovirus (AdV), Epstein-Barr virus (EBV), herpes simplex virus 1 (HSV-1), varicella zoster virus (VZV) and human herpesvirus 6 (HHV-6), assessed in cell culture experiments, is presented in Table 1.

Table 1: Comparison of In Vitro Antiviral Activity of Nucleoside/ Nucleotide Analogs

Virus	EC50s (μM)				
	CMX001	Cidofovir	Ganciclovir	Maribavir	Acyclovir
CMV	0.001	0.4	3.8	0.31	>200
VZV	0.0004	0.5	1.3	No Activity	3.6
HHV-6(B)	0.007	5.4	5.9	ND	100
AdV	0.02	1.3	4.5-33	ND	>100
EBV	0.04	>108	0.9	0.63	8.5
HSV-1	0.06	5.5	0.007	No Activity	2.5
BKV	0.13	115	>200	ND	>200

Study Design

The Phase 2 Study CMX001-201 was a placebo-controlled, dose-escalating trial in HSCT CMV (R+) recipients, evaluating the ability of CMX001 to prevent or control CMV infection. Subjects in five cohorts received either placebo or oral CMX001, in doses ranging from 40 mg weekly (QW) to 200 mg twice weekly (BIW). Subjects post-HSCT were enrolled at the time of engraftment and randomized to CMX001 or placebo (3 to 1 ratio) and received blinded therapy until approximately Day 100 post-transplantation. CMX001 doses were 40 mg QW, 100 mg QW, 200 mg QW, 200 mg BIW and 100 mg BIW. Escalation to the next dose was decided by the Data Monitoring Committee (DMC) after review of the safety data from the previous cohort. Subjects who developed CMV disease or CMV infection requiring pre-emptive therapy with local standard of care were discontinued from blinded therapy and followed for 4 weeks. Subjects who completed treatment with blinded therapy were followed for 8 weeks post-therapy. Subjects were monitored weekly by plasma CMV PCR and urine BKV PCR; plasma was tested by BKV PCR if the urine sample was positive. As part of routine laboratory testing, hematuria and serum creatinine were monitored regularly during the randomized treatment phase.

The primary endpoint of the trial was prevention of CMV reactivation. The results have been presented elsewhere and showed that doses of CMX001 of 100 mg QW and higher had anti-CMV activity.[7] Diarrhea was dose limiting at 200 mg BIW, while lower doses of CMX001 were generally well tolerated with no indication of myelotoxicity or nephrotoxicity.

One key secondary study endpoint was to assess the incidence of other dsDNA virus infections. Results of analyses conducted retrospectively with respect to BKV and its end-organ complications are presented below.

Table 2: CMX001-201 Baseline Subject Characteristics

	BK Positive During Treatment		BK Negative Throughout	
	CMX001 N=94	Placebo N=32	CMX001 N=77	Placebo N=27
Age (years)				
Mean	49.9	49.9	51.8	50.7
Median	50.0	50.0	55.0	53.0
Min, Max	23, 71	21, 68	22, 70	26, 70
Gender, n (%)				
Female	37 (39.4)	12 (37.5)	36 (46.8)	13 (48.2)
Male	57 (60.6)	20 (62.5)	41 (53.3)	14 (51.9)
Race, n (%)				
Asian	6 (6.4)	1 (3.1)	4 (5.2)	1 (3.7)
Black	1 (1.1)	4 (12.5)	2 (2.6)	0
White	84 (89.4)	27 (84.4)	70 (90.9)	26 (96.3)
Other	3 (3.2)	0	1 (1.3)	0
Weight (kg)				
Mean	77.7	84.7	77.1	71.2
Median	77.7	83.3	77.6	70.8
Min, Max	40.6, 131.9	45.4, 146.9	45.5, 127.5	40.8, 110.7
Unrelated donor, n (%)	51 (54.3)	16 (50.0)	46 (59.7)	11 (40.7)
Adult mismatch, n (%)	15 (16.0)	1 (3.1)	12 (15.6)	5 (18.5)
Myeloablative conditioning, n (%)	61 (64.9)	22 (68.8)	48 (62.3)	16 (59.3)
Pre-dose cyclophosphamide, n (%)	44 (46.8)	19 (59.4)	26 (33.8)	7 (25.9)
Pre-dose steroids, n (%)	42 (44.7)	16 (50.0)	27 (35.1)	11 (40.7)

Definitions and Methods

Clinically meaningful end-organ effects were defined as follows:

- Microscopic hematuria: at least 1+ heme noted on urinalysis (dipstick)
- New onset hematuria: at least 1+ heme (confirmed by a consecutive measure of ≥ Trace), occurring during treatment only
- Renal dysfunction at end of treatment – serum creatinine ≥ 120 microM/L (≥ 1.36 mg/dL) at the end of treatment
- New onset renal dysfunction – serum creatinine ≥ 120 microM/L (≥ 1.36 mg/dL) at the end of treatment AND at least 25% greater than baseline serum creatinine

Subjects were tabulated according to treatment group (pooled CMX001 versus placebo) and BKV status (viruria positive or negative any time during treatment). Pairwise comparisons were performed using a Fisher's exact test. Data were pooled for CMX001 versus placebo groups due to the limited sample sizes within individual groups. This approach is conservative since the 40 mg QW dose had no antiviral effect against CMV in the primary analysis. Data from the largest study cohort (CMX001 100 mg BIW) are presented separately in some of the analyses as this dose has been selected for further development of CMX001 in Phase 3 trials.

Among all subjects, 126/230 (55%) had measureable BKV in urine samples at some time during treatment. Of these, 101/126 (80%) were positive at baseline. Cyclophosphamide use as part of the conditioning regimen and male gender were the only parameters differing between subjects with and without BKV infection during the study, consistent with previous reports.

Table 3 presents the extent of BKV viral replication in subjects randomized to CMX001 (including 100 mg BIW) and placebo.

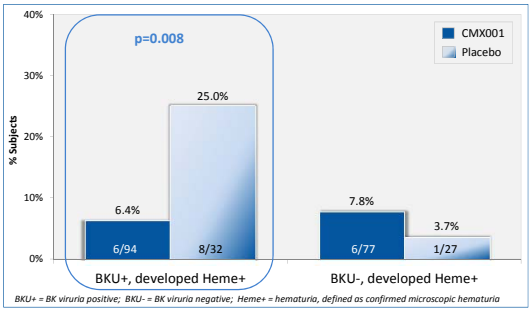
Table 3: Extent of Viruria and Viremia in Subjects Having Positive BKV Viruria at Baseline

	Cohort 4A CMX001 100 mg BIW N=50	Pooled CMX001 Cohorts N=171	Pooled Placebo N=59
Positive urine at baseline	22/50 (44%)	77/171 (45%)	24/59 (41%)
Viruria >1.0E+7 at baseline	15/22 (68.2%)	52/77 (67.5%)	15/24 (62.5%)
Viruria >1.0E+10 at baseline	1/22 (4.5%)	11/77 (14.3%)	4/24 (16.7%)
Viruria >1.0E+10 at any time during treatment	4/22 (18.2%)	26/77 (33.8%)	8/24 (33.3%)
Viruria >1.0E+10 but only at post-treatment week	1/22 (4.5%)	4/77 (5.2%)	1/24 (4.2%)
Viremia at baseline	2/22 (9.0%)	11/77 (14.3%)	3/24 (12.5%)
Viremia at any time during treatment	6/22 (27.3%)	40/77 (47%)	15/24 (46%)
Viremia sustained (≥ 2 consecutive values positive)	5/22 (22.7%)	32/77 (41.6%)	7/24 (29.2%)
Viremia sustained, but no viremia at baseline	3/22 (13.6%)	23/77 (29.9%)	4/24 (16.7%)
Viremia >1000 copies/mL confirmed	4/22 (18.2%)	31/77 (26%)	9/24 (37.5%)
>10,000 confirmed, new onset	0	5/77 (6.5%)	0/24

To explore the impact of BKV infection on emergence of symptoms, the incidence of urinary AEs containing the term BKV in subjects with BKV infection prior to dosing (i.e., BKV PCR positive at Baseline) was analyzed first. Such AEs were rare and reported in 6/77 (7.8%) subjects who received CMX001 as compared to 3/24 (12.5%) of subjects who received placebo.

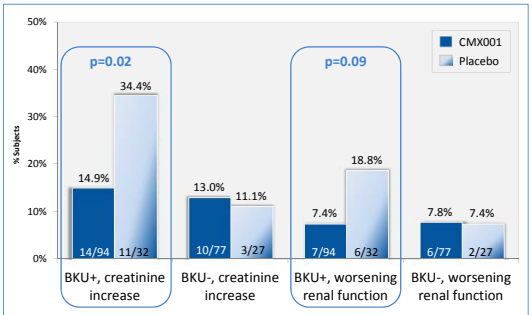
To further explore the impact of CMX001 on HC emergence, the incidence of treatment-emergent hematuria was explored. Results are presented in Figure 1. The impact of CMX001 on renal dysfunction in subjects with preexisting BKV infection is presented in Figure 2.

Figure 1: Exploratory Analysis Suggests CMX001 Reduces Hematuria in Subjects with BKV



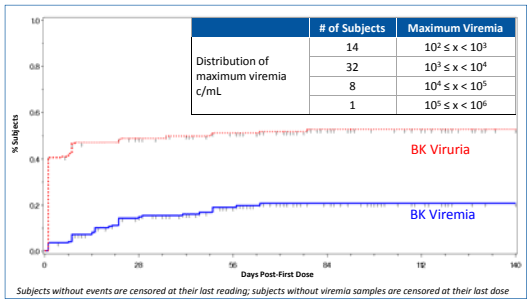
BKU+ = BK viruria positive; BKU- = BK viruria negative; Heme+ = hematuria, defined as confirmed microscopic hematuria

Figure 2: Exploratory Analysis Suggests CMX001 Reduces Renal Impairment in Subjects with BKV



BKU+ = BK viruria positive; BKU- = BK viruria negative; Creatinine increase = creatinine > 120 μM/L
Renal impairment = creatinine increase (creatinine > 120 μM/L) AND 25% increase from baseline at last measurement

Figure 3: Cumulative Incidence of Confirmed BK Viruria and Viremia



Subjects without events are censored at their last reading; subjects without viremia samples are censored at their last dose

Table 4: Association Between Laboratory Abnormalities Indicative of End-Organ Disease and BKV PCR Results in Urine

	Subjects with BKV Viruria				Subjects without BKV Viruria			
	Dysfunction present*		Dysfunction absent		Dysfunction present[3]		Dysfunction absent	
	CMX001	Placebo	CMX001	Placebo	CMX001	Placebo	CMX001	Placebo
Proportion of Subjects (%)	19/94 20%	16/32 50%	75/94 80%	16/32 50%	15/77 20%	4/27 15%	62/77 81%	23/27 85%
P-value[1]	0.003				NS			
Maximum Viruria (c/mL)	2.5×10^8	4.0×10^9	2.5×10^8	7.9×10^7	-	-	-	-
P-value[2]	0.03				-			

[1]*Fisher's Exact test*
[2]*Rank ANOVA interaction p-value (disease*treatment)*
[3]*Laboratory signs of dysfunction defined as having either ≥ 1+ new heme confirmed on urinalysis or last serum creatinine > 120 μM*

Discussion

- BKV reactivation is common post-HSCT and is present at the time of engraftment in more than 40% of the subjects.
- Cyclophosphamide use as part of the conditioning regimen and male gender appear to be associated with BKV reactivation post-HSCT.
- BKV viruria is typically present early post-transplantation while low level viremia tends to develop over the subsequent 8-10 weeks.
- In subjects with BKV reactivation, CMX001 appears to prevent the emergence of hematuria and renal impairment, changes associated with end-organ damage from BKV infection.
- Hematuria and renal dysfunction are rare in HSCT subjects without BKV reactivation and were not different between CMX001-recipients and placebo-recipients, underscoring the lack of nephrotoxicity of CMX001.
- The impact of CMX001 therapy on BKV-induced end-organ disease appears to be related to attenuation of the viral load increases that were associated with emergence of impairment in the placebo recipients over this 8-10 week timeframe .

Conclusion

In subjects with pre-existing BKV infection, CMX001 appears to reduce the incidence of BKV-associated hematuria and serum creatinine elevation, based on exploratory analyses considering objectives measures of end-organ disease. These findings support the utility of CMX001 for broad spectrum antiviral prophylaxis post-transplantation. Moreover, these findings support additional studies of CMX001 in the prevention of HC and BKVAN in HSCT and kidney transplant recipients are warranted.

Acknowledgements

The authors would like to thank the CMX001-201 investigators and DMC, the subjects who participated in the study and all study staff. Chimerix would like to thank, in particular, Thomas Brundage, Senior Director Biostatistics, for conducting the retrospective analyses included in this presentation.

References

1. Gardener SD, Field AM, Coleman DV, Hulme B. New human papovavirus (B.K.) isolated from urine after renal transplantation. Lancet 1971;1:1253-57.
2. Hirsch HH, Knowles W, Dickenmann M, et al. Prospective study of polyomavirus type BK replication and nephropathy in renal-transplant recipients. N Engl J Med 2002;347:488-96.
3. Hirsch H. BK virus: Opportunity makes a pathogen. Clin Infect Dis 2005;41:354-60.
4. Nickeleit V. Animal models of polyomavirus nephropathy: Hope and reality. Am J Transplant 2006;6:1507-09.
5. Pavlakis M, Haririan A, Klassen DK. BK virus infection after non-renal transplantation. Adv Exp Med Biol 2006;577:185-89.
6. O'Donnell PH, Swanson K, Josephson MA, et al. BK virus infection is associated with hematuria and renal impairment in recipients of allogeneic hematopoietic stem cell transplants. Biol Blood Marrow Transplant 2009;15:1038-48.
7. Marty FM, Winston D, Rowley SD, Boeckh M, Vance E. CMX001 for the prevention and control of CMV infection in CMV-seropositive allogeneic stem-cell transplant recipients: A Phase 2 randomized, double-blind, placebo-controlled, dose-escalation trial of safety, tolerability, and antiviral activity. Biol Blood Marrow Transplant 2012;18:S203-204.