of patients achieved CR and the 1-year OS in this group was 43%.

Conclusion: The 5-azacitidine is a treatment modality that can improve or stabilize the disease, allowing time for patients to reach alloHCT, with little toxicity, and can induce response after post-alloHCT relapses.

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Monitoring Changes in Serum Albumin (SA) Concentrations As an Early and Objective Indicator of Potential CMX001-Associated Gastrointestinal (GI) Adverse Drug Effects

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Background: CMX001 is an orally bioavailable, broad spectrum, lipid acyclic nucleoside phosphonate converted inside cells to the active antiviral, cidofovir diphosphate. In the preclinical toxicology program, GI AEs (diagnosed as gastropathy and enteropathy; dose-related changes included flattening or loss of epithelial cells lining the lumen of the small intestine on chronic dosing) were dose-limiting after daily administration; however, there were no GI AEs or gross/microscopic gut changes when animals were dosed twice-weekly (BIW) up to 9 months. Radiolabel studies in mice confirmed that CMX001 concentrates in the gut mucosa more than in other tissues. In a Phase 2 dose-escalation study (CMX001-201; ClinicalTrials.gov identifier: NCT00942305) evaluating CMX001 for CMV prophylaxis in allogeneic hematopoietic stem cell transplant (HSCT) recipients, an increased rate of profuse watery diarrhea was seen at 200 mg BIW and was considered dose-limiting in this population. A program-wide safety monitoring and management plan that included an option for dose interruption ($\leq$ 2 weeks) in subjects with $\geq$ Grade 3 diarrhea was introduced. Subsequently, few subjects ($\leq$ 10%) discontinued therapy because of GI AEs, indicating that dose interruption is an appropriate strategy to manage CMX001-associated GI AEs and to achieve effective CMV suppression in this population.

Methods: Serum chemistry data were evaluated for changes in SA, a well-established marker of protein loss, to assess the potential relationship to diarrhea. Abnormally low SA concentrations were tabulated and the lowest value identified through +1 week post treatment. A clinically meaningful SA decrease was defined as value $\leq$ 30 g/L (lower limit of normal 33 g/L) and $\geq$ 4 g/L lower than baseline.

Results: Increased grade and/or duration of diarrhea correlated with the decrease in SA concentrations over time as shown in the Kaplan-Meier plots with data grouped by "low" ($\leq$ 100 mg/week) and "high" ($\geq$ 200 mg/week) CMX001 dose vs. placebo. To rule out GI-GVHD (a common cause of diarrhea in HSCT recipients), the SA data from solid organ transplant (SOT) patients treated with CMX001 in an expanded access study (CMX001-350; ClinicalTrials.gov ID: NCT01143181) were also evaluated. A similar timing of decrease in SA concentrations was seen in these subjects who are unlikely to have GVHD; urinalysis data also excluded proteinuria as a cause.

Conclusions: Our clinical experience in the HSCT population is consistent with preclinical findings. On chronic dosing, CMX001 likely accumulates in the gut mucosa in some patients and causes diarrhea that may be more pronounced in individuals with other causes of diarrhea (eg, GI-GVHD). Dose interruption gives the gut mucosa time to recover, allowing subjects the opportunity to resume therapy. Monitoring SA changes in patients may provide an early and objective indicator of potential drug-related GI AEs.

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Renal Safety of Broad Spectrum Antiviral CMX001 in the Prevention of CMV Infection Post- Allogeneic Hematopoietic Cell Transplantation (HCT)

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Background: CMX001 is an orally bioavailable, broad spectrum, lipid acyclic nucleoside phosphonate converted intracellularly into the active antiviral, cidofovir diphosphate. Unlike cidofovir, CMX001 is not a substrate for the anion organic transporter and therefore is not concentrated in the kidney.

Methods: Study CMX001-201 was a 9-11 week randomized, placebo-controlled, double-blind, dose-escalation study (evaluating 40 mg weekly [QW], 100 mg QW, 200 mg QW, 200 mg twice-weekly [BIW] and 100 mg BIW) of CMX001 for the prevention of CMV infection post-HCT (ClinicalTrials.gov ID: NCT00942305). Treatment was initiated at the time of engraftment and continued until Week 13 post-HCT. Results presented elsewhere have shown that CMX001, at various doses, was active and well tolerated in the prevention of CMV infection or disease. Renal safety was assessed throughout the duration of therapy using serum creatinine, urinalysis and estimated glomerular filtration rate (GFR, MDRD4 formula).

Results: 230 subjects were enrolled in the study; 59 received placebo and 171 received CMX001 at various doses. 24 subjects (41%) on placebo and 77 subjects on CMX001 (45%) had BK viruria prior to dosing. One subject discontinued CMX001 40 mg QW due to acute renal failure; no other subject discontinued from the study due to renal adverse events. Results of calculated GFR by Study Cohort and over time are presented in Table 1 below. Overall, renal function tended to decline in placebo recipients while renal function appeared to improve in subjects who received CMX001 at 200 mg per week (either QW or divided into 2 BIW doses). The renal function decline in placebo recipients appeared to be associated by the presence of BK virus (BKV) in the urine at the time of treatment commencement, while the proportion of subjects with renal dysfunction was similar between BKV positive and negative subjects among CMX001 recipients. There was also a decreased incidence of microscopic hematuria in BKV infected subjects treated with CMX001 as compared to placebo recipients (6% vs. 25%).

Conclusions: CMX001 when administered at doses of 200 mg per week is not associated with signs of nephrotoxicity

Table 1
Study 201: Mean (N) Change from Baseline in GFR (mL/min/1.73m^2) by Visit and Dose

Visit	Placebo	CMX001 40 mg QW	CMX001 100 mg QW	CMX001 200 mg QW	CMX001 100 mg BIW
Week 2	-6.5 (56)	-7.7 (23)	-11.6 (26)	-9.5 (37)	-4.5 (49)
Week 4	-8.7 (46)	-9.4 (19)	-8.6 (25)	-12.4 (31)	-3.3 (44)
Week 6	-10.1 (35)	-7.0 (13)	-12.0 (22)	-1.9 (24)	1.3 (33)
Week 8	-18.5 (36)	-2.2 (12)	-11.3 (19)	5.8 (18)	12.2 (31)*
Week 10	-15.4 (21)	-7.3 (5)	-15.6 (13)	5.7 (14)	6.1 (21)*
Post-Week 1	-13.3 (57)	-5.8 (19)	-2.8 (25)	8.8 (35)	7.7 (49)*

* $P < 0.05$ t-test versus placebo