



Pre-engraftment Initiation of Brincidofovir (CMX001) in Hematopoietic Cell Transplant Recipients is Supported by Lack of Myeloid Toxicity

G Papanicolaou¹, M Grimley², M Morrison³, T Brundage³, H Mommeja-Marín³

1. Memorial Sloan-Kettering Cancer Center, New York, NY
2. Cincinnati Children's Hospital Medical Center, Cincinnati, OH
3. Chimerix, Inc., Durham, NC

Background:

Brincidofovir (BCV, CMX001) is a nucleotide analog in Phase 3 development for the prevention of cytomegalovirus (CMV) infection following hematopoietic cell transplantation (HCT), with broad-spectrum activity against double stranded DNA (dsDNA) viruses. Currently available antivirals with anti-CMV activity have been associated with myeloid toxicity in HCT recipients limiting treatment initiation until after engraftment, and increasing the risk of graft failure during treatment. Use of antivirals with known drug-related neutropenia in HCT recipients has resulted in increased rates of invasive bacterial and fungal infections.

Methods:

Absolute neutrophil counts (ANC) were compiled from HCT recipients enrolled in two placebo-controlled and one open-label clinical trial of BCV. Study 201 was a placebo-controlled dose escalation study of BCV for the prevention of CMV infection, with study drug initiated in the first 35 days post-HCT; only subjects receiving a total weekly dose of 200 mg in Study 201 were included in this analysis. Study 202 was a placebo-controlled study of BCV for preemptive treatment of adenovirus (AdV) viremia with study drug initiated a median of 55 days post-HCT. Study 350 was an expanded access study for treatment of subjects with a serious or life-threatening infection with one or more dsDNA viruses and no therapeutic options. As previously presented, Study 201 showed that BCV was active in the prevention of CMV infection or disease, and Study 202 showed that BCV 100 mg BIW decreased AdV viremia and had potential benefit in all-cause mortality.

In this analysis, ANC were evaluated in subjects with baseline (BL) ANC of <1500 cells/ μ L, who did not receive concomitant valganciclovir (vGCV) or ganciclovir (GCV). Last on-treatment ANC values and maximum on-treatment ANC values were compared to baseline. Subjects from Study



201 who received BCV 200 mg/wk and all subjects from Study 202 were pooled and compared to those subjects receiving placebo (PBO). Only those Study 350 subjects that were post-HCT were included in the analyses.

Graft failure rates were also evaluated in these three studies.

Results:

In Studies 201 and 202, 25% (49 of 200) subjects had ANC <1500 cells/ μ L at BL. Nine subjects were excluded from further analysis due to concomitant GCV or vGCV use. Of the remaining 40 subjects, 24 were randomized to BCV and 16 to PBO. Subjects received a mean 6.0 (PBO) to 6.5 weeks (BCV) of treatment. Recovery of neutrophil count to > 1500 cells/ μ L during treatment occurred in 83% (20 of 24) subjects on BCV compared to 81% (13 of 16) on PBO. Numerically improved neutrophil count (> BL) was noted in 92% (22 of 24) BCV-treated subjects, compared to 94% (15 of 16) on PBO. Due to the clinical importance of early ANC recovery, similar analyses were performed for the first four weeks of study drug treatment: 68% BCV subjects versus 75% PBO subjects achieved ANC > 1500 at week 4, while 83% BCV subjects versus 81% PBO subjects had an improved ANC > BL. Observed ANC through the first four weeks revealed a maximum ANC > 1500 in 79% of BCV subjects compared to 81% of PBO subjects; evidence of early neutrophil recovery with a maximum ANC > BL was observed in 88% of BCV subjects compared to 94% of PBO subjects.

In open-label Study 350 of patients with life-threatening dsDNA infection, 41 subjects were post-HCT with ANC <1500 cells/ μ L at BL. Prior vGCV or GCV use was reported in 41%, and 27% subjects were enrolled due to concerns related to cytopenia. Fourteen subjects were excluded due to concomitant vGCV or GCV use. The remaining subjects received BCV for a median of 4 weeks, and 19/27 (71%) had last on-treatment ANC > 1500, and 21/27 (78%) had last on-treatment ANC > BL. Maximum ANC recorded during therapy was >1500 in 23/27 (85%), and was > BL in 25/27 (93%).

In studies 201 and 202, graft failure was reported in 2/123 (1.6%) subjects on BCV, versus 4/77 (5.2%) subjects on PBO. In study 350, graft failure was reported in 1 (4%) subject on BCV monotherapy, versus 3/14 (21%) on BCV plus GCV/vGCV.



Conclusions:

These data suggest BCV has minimal negative impact on neutrophil recovery, supporting initiation of BCV in the immediate post-transplant period and prior to engraftment in the current Phase 3 SUPPRESS trial. The hematologic safety profile of brincidofovir and earlier initiation of antiviral prophylaxis in the post-transplant period may provide improved efficacy in the prevention of CMV viremia and disease post-HCT.