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

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Introduction

Currently available antivirals with anti-CMV activity have been associated with myeloid toxicity in HCT recipients, limiting treatment initiation until after engraftment, and increasing risks of bacterial and fungal infections. Reactivation of latent CMV has been reported as early as day 10 post-HCT, and is not uncommon prior to demonstrated engraftment. Brincidofovir (BCV), currently in Phase 3 development for prevention of CMV infection post-HCT, is a nucleotide analog with broad-spectrum antiviral activity against dsDNA viruses and a favorable safety profile.

Methods

- Absolute Neutrophil Counts (ANC) from post-HCT subjects across three studies were evaluated
  - CMX001-201 (201): a placebo controlled, dose escalation study of BCV for the prevention or preemption of CMV post-HCT in adult subjects
  - CMX001-202 (202): a placebo controlled study of BCV as preemption of adenovirus (AdV) post-HCT in adult and pediatric subjects
  - CMX001-350 (350): an expanded-access study for treatment of serious/life-threatening dsDNA viruses in adult and pediatric subjects with no/limited therapeutic options

- The following criteria were used for inclusion of subjects in the analysis:
  - Post-HCT subjects who received a total weekly BCV dose of 200 mg for adults (or 4 mg/kg for children), or placebo (PBO)
  - Baseline (BL) ANC value was available, and <1500 cells/µL (BL was defined as the last value on or before the day of first dose)

- The following analyses were conducted:
  - Last on-treatment ANC values were compared to BL (on-treatment values used were the minimum value within the window for on-treatment visits)
  - Maximum on-treatment ANC values were compared to BL
  - Last and maximum on-treatment ANC values within the first 4 weeks of treatment were compared to BL
  - Clinical events of secondary graft failure, as defined by the investigator were evaluated

Demographics and Baseline Characteristics

	201/202 BCV (n=25)	201/202 Placebo (n=16)	350 BCV (n=33)	350 BCV + (v)GCV* (n=8)
Age (yrs)				
Median (Range)	37 (1-69)	47 (2-67)	22 (0-69)	44 (0-65)
Age Range, n (%)				
< 2 yrs	2 (8%)	0	4 (12%)	1 (13%)
2 to 11 yrs	3 (12%)	1 (6%)	8 (24%)	2 (25%)
12 to 17 yrs	0	1 (6%)	1 (3%)	0
18 to 65 yrs	19 (76%)	13 (81%)	16 (48%)	4 (50%)
≥65 yrs	1 (4%)	1 (6%)	4 (12%)	1 (13%)
Gender, n (%)				
Female	9 (36%)	7 (44%)	7 (21%)	2 (25%)
Male	16 (64%)	9 (56%)	26 (79%)	6 (75%)
Race, n (%)				
Asian	1 (4%)	1 (6%)	0	0
Black	4 (16%)	0	4 (12%)	0
White	20 (80%)	15 (94%)	23 (70%)	7 (88%)
Other	0	0	6 (18%)	1 (13%)
Weight (kg)				
Median (Range)	75 (10-128)	76 (15-147)	59 (8-113)	61 (4-83)
Days from HCT				
Median (Range)	27 (8-139)	23 (14-78)	74 (1-1765)	120 (1-412)

*BCV + (v)GCV = BCV + ganciclovir or valganciclovir

Acknowledgements

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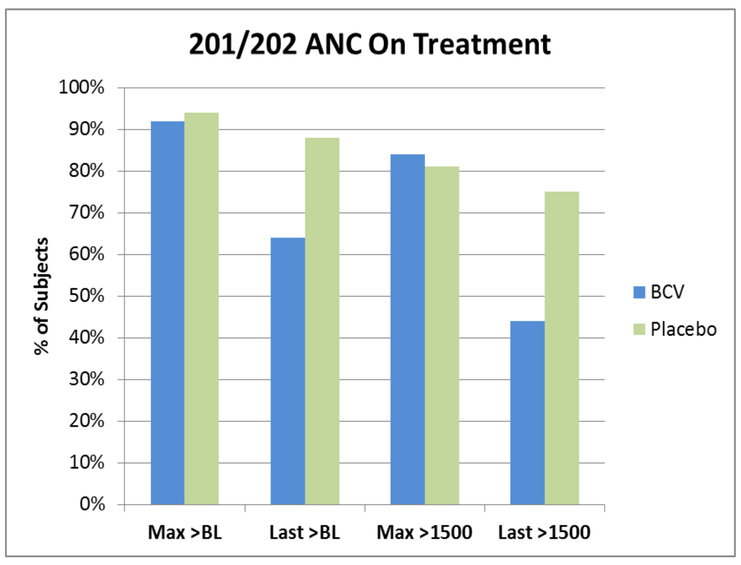
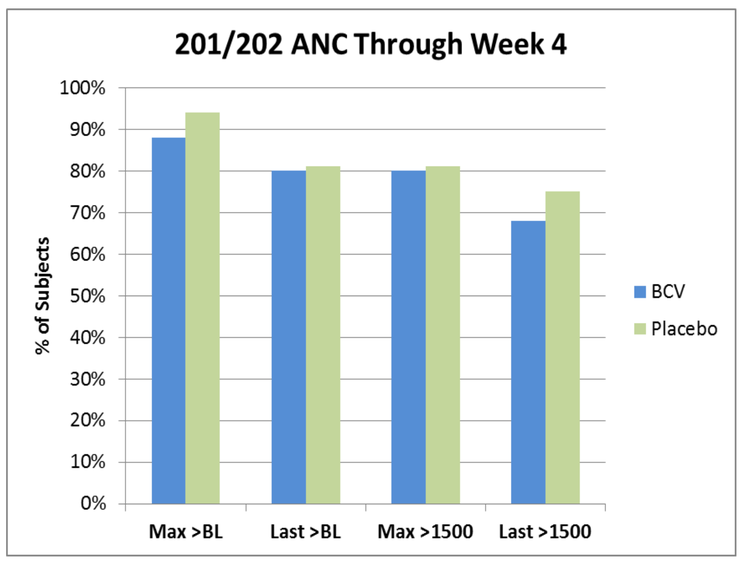
Results

CMX001-201/CMX001-202 Analysis

Of the 41 pooled subjects from studies 201 and 202 that were evaluated, 25 received BCV 200mg/week and 16 received PBO. Subjects in the two groups were treated for a median 47 and 22 days, respectively.





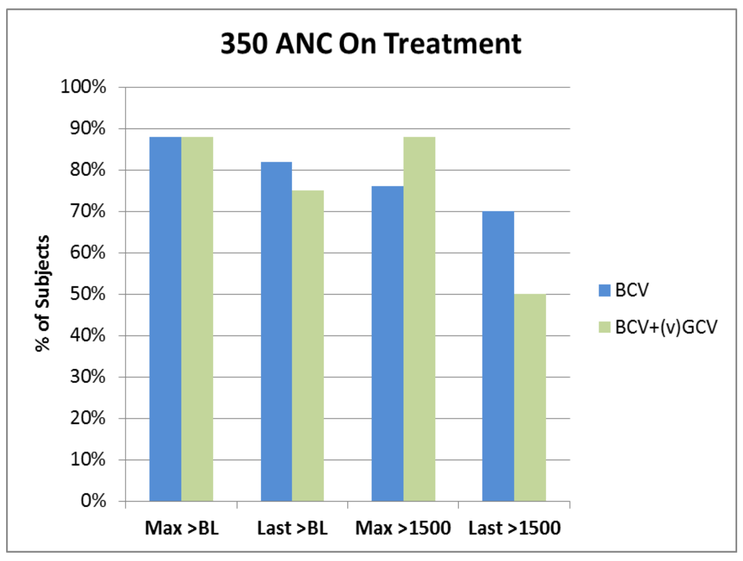
Clinical graft failure rates in 201/202:
- BL ANC <1500 cells/µL: No BCV subjects, compared to 6.3% PBO subjects
- Regardless of BL ANC: 1.8% BCV subjects, compared to 4.3% PBO subjects

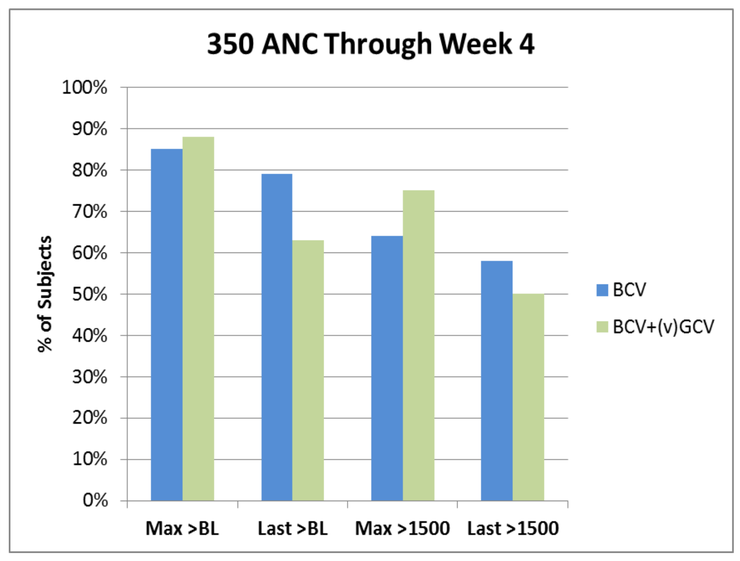
Clinical Graft Failure	201/202 BCV	201/202 Placebo
BL ANC <1500	0 / 25	1 / 16 (6.3%)
All Subjects	2 / 112 (1.8%)	3 / 69 (4.3%)

CMX001-350 Analysis

In study 350, 41 post-HCT subjects had baseline ANC values <1500 cells/µL:
- 17/41 (41%) reported prior GCV or vGCV use
- 11/41 (27%) reported cytopenia or myelotoxicity as a reason for enrollment in the study

Thirty-three subjects used BCV as monotherapy (BCV), while 8 subjects reported concomitant use of GCV or vGCV with BCV (BCV+(v)GCV). Subjects in the 2 groups were treated for a median 29 and 57 days, respectively.





Clinical graft failure rates in 350:
- BL ANC <1500 cells/µL: 6.1% of BCV monotherapy subjects, compared to 25% of those on BCV+(v)GCV
- Regardless of BL ANC: 1.7% of BCV monotherapy subjects, compared to 7.1% of those on BCV+(v)GCV

Clinical Graft Failure	CMX001-350 BCV	CMX001-350 BCV + (v)GCV
BL ANC <1500	2 / 33 (6.1%)	2 / 8 (25.0%)
All Subjects	2 / 119 (1.7%)	2 / 28 (7.1%)

Conclusions

- Brincidofovir appears to have no negative impact on neutrophil recovery in this analysis of HCT recipients from two PBO-controlled trials, and less negative impact on neutrophils when administered as monotherapy than when combined with GCV or vGCV.
- Although there were few secondary graft failures reported in the combined PBO-controlled trials and the expanded-access Study 350, there was no evidence of an increased risk of graft failure in subjects exposed to brincidofovir. The risk of graft failure secondary to infection with a dsDNA virus may be lower in subjects administered brincidofovir.
- Brincidofovir's lack of hematologic or myeloid toxicity supported the current study design of the Phase 3 SUPPRESS trial, including initiation of treatment in the immediate posttranplant period regardless of engraftment.
- If hematologic safety is confirmed in the ongoing SUPPRESS trial, initiation of brincidofovir in the peritransplant period could have a significant impact on the rates of CMV reactivation in at-risk HCT recipients.