ADENOVIRUS (ADV) VIROLOGIC RESPONSE TO BRINCIDOFOVIR IN PATIENTS WITH EVIDENCE OF RESISTANCE

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Background: Following oral delivery, brincidofovir (BCV, CMX001) is converted intracellularly to the active antiviral cidofovir (CDV) diphosphate. BCV shares the broad-spectrum antiviral activity of CDV against dsDNA viruses, including AdV and is in Phase 3 development for AdV. Mutations in the AdV DNA polymerase gene (AdV pol) can impart resistance in vitro to CDV and BCV. Here we report on the effect of mutations associated with CDV/BCV resistance on the clinical response to BCV.

Methods: BCV resistant isolates of AdV were selected in vitro by passaging and evaluated by AdV pol gene sequencing and phenotyping. Immunocompromised subjects with suboptimal virologic responses in Study CMX001-202 (which evaluated pre-emptive BCV therapy for asymptomatic patients with AdV viremia) and CMX001-304 (which is assessing the activity of BCV as treatment for clinically significant AdV infections) were evaluated by sequencing the AdV polymerase gene.

Results: Serial passage of AdVC5 with BCV selected viruses with mutations at T87I and/or V303I in AdV pol and resistance in vitro. Each mutation was identified in one patient undergoing treatment for AdV. T87I was found in conjunction with 3 other changes in AdV pol at baseline and on-therapy in CMX001-304 (n=1). The plasma viral load (pVL) for this subject was 8.2 x 10^5 copies/mL (c/mL) at baseline, dropped 1.5 logs by Week 2, but then increased to 1.7 log above baseline by Week 8. Restart of IV CDV was ineffective, with pVL rising to 7.6 log at Week 8. BCV was restarted, and pVL declined to <100 c/mL by Week 12, when AdV was also cleared from stool and respiratory secretions. One subject in CMX001-202 had a treatment-emergent V303I detected at Week 11 in the context of six other changes in AdV pol. Plasma VL decreased by >2.7 logs from baseline after 1 week of BCV, but was ~10^3 c/mL until Week 8 when it increased to >10^4 c/mL in conjunction with emergence of the V303I mutation.

Conclusions: These cases provide preliminary genetic evidence for an in vivo antiviral effect of BCV against AdV that is mediated by the viral polymerase. Prior use of CDV may predispose patients to have BCV resistant AdV emerge, but the emergence of virus with known resistance to BCV in vitro may not always correlate with virologic failure. The antiviral efficacy of BCV in the face of low level resistance, immune recovery, or other factors will be examined in the AdVise study.