Resistance Profile of Adenovirus Exposed to Brincidofovir In Vitro and In Vivo

Author Block: P. Sethna, A. Bae, T. Brundage, H. Mommeja-Marin, M. Berrey, **R. Lanier**; Chimerix, Inc., Durham, NC

Abstract:
Background:
Brincidofovir (BCV, CMX001) is an orally bioavailable lipid acyclic nucleoside phosphonate which is converted intracellularly to the active antiviral cidofovir diphosphate (CDV-PP). BCV shares the in vitro broad-spectrum antiviral activity of CDV against all five families of dsDNA viruses which cause disease in humans, including adenoviruses (AdV). AdV resistance to BCV in vitro and in Study 202 was analyzed to explore the potential role of viral resistance in AdV response to BCV.

Methods:
Human AdVC5 was passaged in vitro on A549 cells in the presence of increasing concentrations of BCV or CDV for more than five months (15 passages). AdV DNA polymerase (pol) genotype and viral phenotype were determined using standard methods. An exploratory Phase 2 study (Study 202) screened allogeneic HCT recipients for AdV viremia: patients with asymptomatic AdV PCR ≥ 100 c/mL were randomized to placebo, BCV once weekly, or BCV twice weekly (N=48). Plasma samples were evaluated for AdV viremia by Viracor-IBT. Genotypic analysis of AdV pol was performed for non-responders and subjects with viral rebound (virologic failure [VF]).

Results:
In vitro, AdV passaged with BCV or CDV exhibited a 4 to 8-fold increase in EC50 versus wild-type virus after 15 passages. Genotyping identified two mutations (T87I & V303I) in AdV polymerase from BCV passaging and one (T1151I) from CDV passaging. In Study 202, V303I was detected in AdV from one subject with VF at Week 12 of twice weekly BCV. Of the 48 subjects enrolled in the study, twelve treatment-emergent mutations (TEMs) were identified in AdV pol from seven subjects with virologic failure. No unique TEM change was found in more than one subject.

Conclusions:
The in vitro resistance profile of AdVC5 demonstrates that several mutation patterns can confer low to moderate resistance to BCV, but that resistance is slow to emerge. The in vivo AdV resistance profile is being explored and identified one mutation observed in vitro and several mutations not seen during in vitro passage. Notably, prior antiviral reporting was not mandatory in Study 202 beyond 30 days prior to dosing, so the extent of prior CDV use is unknown. Three subjects had a recorded history of CDV use and two of these experienced VF; therefore, the results from Study 202 do not reflect a CDV naïve population.