Conference: 27th ASGCT Annual Meeting 2024

Title: *Pharmacokinetics and Vector Shedding in NHPs Following a Single Intravenous Infusion of a CD20-targeted Engineered Lentiviral Vector*

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Lentiviral vector (LVV) based ex vivo cell therapy is well established, and in this setting the carryover of infectious LVV particles into patients is low for clinical-grade material (Cesani et al. 2015). The in vivo administration of LVV to generate CAR cells inside the patient has the potential to circumvent manufacturing and administration challenges presented by ex vivo cell therapies but presents a potential risk of environmental contamination through shedding of infectious vectors in patient excreta. We developed an engineered replication-incompetent LVV clinical candidate (INT2104) that directs in vivo production of CD20-directed CAR-T and CAR-NK cells following a single-dose

intravenous (IV) infusion. Here we report pharmacokinetics of vector capsid protein and RNA genomes in blood, and shedding of vector RNA genomes in urine, feces, and saliva of cynomolgus macaques after IV administration of 2 x 109 transducing units of INT2104. This dose represents the highest dose proposed for a FIH study planned to start in 4Q2024.

We used ELISA and RT-qPCR methods to detect vector capsid protein and RNA genomes respectively in several LVV studies in cynomolgus macaques, including the GLP-Toxicology study. In all studies, LVV drug product was administered in a single-dose IV infusion. LVV capsid protein peaks in the blood 1 day after vector administration and is then rapidly cleared. Vector RNA genomes are cleared more rapidly than protein and are detected at much lower levels than expected if the all the capsid protein measured in circulation were associated with intact LVV particles. These data indicate that clearance of intact and therefore potentially infectious vector particles from circulation is rapid after IV administration of our replication-incompetent LVV.

Shedding of vector RNA genomes into feces, saliva and urine was detectable in some animals at very low levels in the first 3 days following vector administration, suggesting very limited and transient LVV shedding. Taken together these data demonstrate rapid clearing of an in vivo- administered replication-incompetent LVV, with limited shedding in animal excreta indicating low risk of environmental contamination.