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Assay Development and PK-PD in Phase 1 Virotherapy with Oncolytic Vaccinia Virus (JX594) for Hepatic Cancer Patients

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JX594 is oncolytic virus which was modified from Wyeth strain of vaccinia virus. With this genetic modification, JX594 replicates selectively in cancer cells and induces tumor specific cytotoxic T lymphocytes. Phase I, single-center, dose-escalation study of JX-594 administered by intratumoral injection in patients with refractory solid tumor(s) located within the liver is being done in our institution. Primary objectives are to determine the safety and MTD/MFD. Secondary objectives include determination of JX-594 PK replication and shedding, and injection site tumor responses. Assay development was done to measure circulating viral genomes in whole blood and plasma samples from each patient using an analytical method based on real-time quantitative polymerase chain reaction (QPCR) using a TaqMan MGB-fluorescently-labeled probe. Limit of Quantitation (LOQ) and Limit of Detection (LOD) were determined. Based on this LOD and LOQ, preliminary information regarding PK-PD was illuminated. As expected, each patient had circulating virus detected in the blood immediately after injection (15 and/or 30 minutes). Genomes were rapidly cleared and were undetectable by 4~6 hours post-dose in all but a single cycle. Two of five patients showed a second peak of virus above the LOQ on both Day 5 and Day 8 or 15; this pattern of clearance followed by the re-emergence of detectable genomes is consistent with virus replication. Total estimated genomes in circulation were as high as $1.2 \times 1{,}010$ genomes on Day 5 in one patient; this number of genomes is higher than the original dose1. Genomes were above 3×107 genomes on at least one time point in three patients, and eight total time points, including as early as study Day 5 in two patients. Patients tolerated this viremia well without clinically significant sequelae. Preliminary summary of PK-PD analysis will be presented.

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