

A Phase I/II Dose Escalation Study of TKM-080301, a RNAi Therapeutic Directed Against PLK1, in Patients with Advanced Solid Tumors, with an Expansion Cohort of Patients with NET or ACC

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Background: Polo-like kinase 1 (PLK1) regulates multiple critical aspects of cell progression, is highly expressed in many human tumors and its expression correlates negatively with patient outcome. TKM-080301 is a lipid nanoparticle formulation of a small interfering RNA (siRNA) directed against PLK1.

Methods: This phase I/II open-label study is ongoing in patients with advanced solid tumors or lymphoma, with an expansion cohort of patients with neuroendocrine tumors (NET) or adrenocortical carcinoma (ACC). During dose escalation, sequential cohorts of 3 to 6 patients received TKM-080301 as a 30-minute IV infusion on Days 1, 8, and 15 of a 28-day cycle. Primary objectives include determination of safety, maximum tolerated dose (MTD) and dose limiting toxicities (DLTs). Secondary objectives include characterization of pharmacokinetics (PK) and preliminary assessment of anti-tumor activity and pharmacodynamic effects. Pre- and post-dose biopsy samples are being collected from consenting patients.

Results: Thirty-six (36) patients have been treated at doses ranging from 0.15-0.9 mg/kg/week. The most common drug-related adverse events have been mild-to-moderate delayed infusion related reactions, pyrexia, chills, nausea, vomiting, and fatigue. Mild, transient increases in cytokines have been observed at ≤ 0.75 mg/kg/week and generally correlated with the timing of these reactions. DLTs were observed at 0.9 mg/kg/week and included hypoxia/dyspnea and thrombocytopenia. Pharmacokinetics were dose proportional for C_{max} and AUC with no obvious accumulation. Three patients have received TKM-080301 for at least 6 months (6 cycles) with no cumulative toxicity, including one patient (appendiceal NET) with a durable (11 months) confirmed partial response, and two patients with stable disease (ACC and one colon). Two others had stable disease; an ACC patient and an appendiceal NET patient who also had a reduction (~55-60%) in chromogranin A from pre-treatment levels.

Conclusions: Preliminary results from this first-in-human trial indicate TKM-080301 was generally well-tolerated by the majority of patients. Preliminary antitumor efficacy has been observed, supporting PLK1 as a therapeutic target. Two DLTs were observed at 0.9 mg/kg/week and patient accrual is ongoing at 0.75 mg/kg/week in an expansion cohort with enrollment restricted to patients with NET or ACC.