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“Dose-escalation phase I study of NKTR-105, a novel pegylated form of docetaxel”

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Abstract:

Background: Docetaxel (D) is widely used in the treatment of several solid tumor malignancies. It has a relatively short half-life of 11 hours. NKTR-105 was engineered to provide a sustained release of D to improve its efficacy, safety, and tolerability profile over marketed D. Pharmacokinetic (PK) studies in rats and dogs showed that NKTR-105 improved the D PK profile by reducing its peak concentrations and prolonging its half-life. NKTR-105 demonstrated superior activity over D in mouse models of human lung, colon, and prostate carcinomas. In PK-PD studies, NKTR-105 resulted in sustained D concentrations in plasma and tumor. Equitoxic doses of D and NKTR-105 achieved similar plasma D AUC, but tumor AUC was 2-fold greater after NKTR-105 administration, indicating that the superior antitumor activity of NKTR-105 was mediated by greater and sustained tumor D exposure. The encouraging antitumor activity and unique PK profile formed the basis for the design and initiation of study 08-PDX-01, a phase I, multicenter, open-label, dose-escalation study to assess the safety, tolerability, and pharmacokinetics of NKTR-105 when given on a Q21 day schedule. **Methods:** The primary objective of this first Phase 1 study is to characterize the safety profile of NKTR-105 and establish a maximum tolerated dose (MTD) of NKTR-105 when given on an every 21-day treatment schedule as 1-hr intravenous infusion. Secondary objectives include determination of the plasma PK profile of NKTR-105 and its metabolite docetaxel and exploratory evaluation of antitumor activity. Patients who are ≥ 18 years old and who have a histologically confirmed, evaluable, or measurable solid tumor that is metastatic or unresectable, for which standard curative or palliative therapies do not exist are eligible. Each cohort of 3 to 6 patients is treated at a single dose level of NKTR-105. Doses are escalated in 25% to 100% increments based on adverse and serious adverse events, dose limiting toxicities, laboratory and PK data. Once the MTD has been identified, a total of up to 20 patients may be treated at that dose to further evaluate the safety, anti-tumor effect and PK of NKTR-105. To date, 17 patients have been enrolled in the study.