Population Pharmacokinetics of NKTR-102, a Topoisomerase I Inhibitor-Polymer Conjugate in Patients With Advanced Solid Tumors

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Abstract

Background: NKTR-102 demonstrates significant anti-cancer activity in a wide variety of tumor models in vivo. It is a novel, topoisomerase I inhibitor-polymer conjugate designed to achieve a more favorable pharmacokinetic (PK) profile compared to its active metabolite SN38, which is a potent DNA intercalator that is rapidly excreted. NKTR-102 is a prodrug that is non-toxic to normal cells and has been shown to be 100-1000 times more potent than SN38.

Methods: A phase 1 study (NKTR-102-101A) was conducted in patients with advanced solid tumors, including breast, ovarian, and colorectal cancers. NKTR-102 was administered as a 90-min IV infusion at doses of 58-245 mg/m². Pharmacokinetic analysis was performed using non-linear mixed effects modeling. Individual patient concentrations in the per-protocol set were analyzed for all analytes using a 2-compartment pharmacokinetic model with either zero-order input for NKTR-102 or first-order input for all metabolites, and first-order output for SN38 and SN38-G. The model was parameterized using patient covariates and the effects of cetuximab on SN38-G clearance were explored. The models were used to simulate population pharmacokinetic and pharmacodynamic (PD) profiles.

Results: A total of 94 patients were enrolled in the study. NKTR-102 was well tolerated and led to inhibited tumor growth in a wide range of murine models. The PK characteristics of NKTR-102 and its metabolites were consistent with previously reported data. The results of the PK analysis demonstrate that NKTR-102 has superior activity compared to irinotecan in a wide range of mouse models of human xenograft tumors. The PK in patients with ovarian cancer is similar to those with all other cancers, suggesting that the current treatment regimen might be appropriate for this patient population.

Conclusions: NKTR-102 has superior activity compared to irinotecan in a wide range of mouse models of human xenograft tumors. The PK in patients with ovarian cancer is similar to those with all other cancers, suggesting that the current treatment regimen might be appropriate for this patient population.