Dose escalation safety study of Nanotax® in dogs

Kim A. Selting[1], Charles Decedue[2], Carolyn J. Henry[1], Sandra Axiak[1]

[1]University of Missouri, Columbia, 900 E. Campus Dr., Columbia, MO 5211, [2]Crititech, Inc. 1321 Wakarusa Dr., Suite 2102, Lawrence, KS 66049

The goal of this project is to determine the suitability of CritiTech's existing formulation of fine-particle paclitaxel, Nanotax®, for the treatment of spontaneously-occurring cancer in dogs. The rationale behind this project is that paclitaxel is highly effective in the treatment of human cancers, but cannot be used in dogs because of their exquisite sensitivity to the solubilizing agents (e.g., CremophorEL®) used in commercially available formulations. Abraxane®, a paclitaxel coated with human serum albumin (HSA), is also unsatisfactory because the HSA induces an immune reaction in canines. CritiTech has demonstrated that Nanotax® increases overall survival in a mouse xenograft model of ovarian cancer and indeed has initiated Phase I human trials of the drug. To accomplish the objectives of this application, two specific aims will be pursued: (1) determine the maximally tolerated dose and assess the toxicities of Nanotax® administered to dogs by intravenous injection, and (2) determine the plasma pharmacokinetics of Nanotax® administered intravenously to dogs. Clinically normal dogs (n=3) were treated with increasing amounts of Nanotax® while monitoring clinical signs of toxicity via physical examination and laboratory evaluation. Serial plasma samples were collected and analyzed for paclitaxel content to determine pharmacokinetic parameters for each dose level. Preliminary evaluation suggests that pharmacokinetic parameters are dose-linear and that the drug is rapidly cleared from circulation. The circulating half life is short which may be a result of clearance by the reticuloendothelial system. Final postmortem evaluation will be performed to determine whether the drug has accumulated in any organ system. We will use data generated to determine an appropriate starting dose for a Phase I/II study of Nanotax® in tumor-bearing dogs to determine tolerability in a patient population and efficacy against various canine cancers.