Tumor size was monitored with digital caliper during the study.

In Vivo Efficacy and Enhanced Tumor Accumulation of Liposomal Vinorelbine (TLC178) in Human Sarcoma Xenograft Mouse Models (FPN 1722P)

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BACKGROUND

Soft Tissue Sarcoma (STS) is a rare and heterogeneous group of malignant tumors affecting 2.86 per 10,000 people in the EU. STS arises in connective tissue and can develop at any age, most often in middle-aged and older adults, with a sex ratio of 1.2:1.2. Approximately half of STS patients with intermediate or high grade metastatic disease require systemic treatment.2

Vinorelbine (VNB) is a member of vinca alkaloid medications and approved for the treatment of non-small-cell lung cancer as well as off-label use for metastatic breast cancer over 20 years and beyond upon FDA-approved indication. The anti-tumor activity of VNB is primarily due to inhibition of mitosis through its binding to tubulin and disrupting formation of mitotic spindles.3 It has also been reported to be an active chemotherapy agent in previously treated STS or advanced STS patients.4

Liposomal VNB (TLC178) is a novel unilamellar sustained release liposomal formulation with a narrow particle size distribution. The surface of the liposome is modified with the designed polymer to avoid mononuclear phagocytosis. TLC178 is developed with the potential to decrease toxicity, improve tolerability and increase durable response rates. In the presented preclinical studies, TLC178 resulted in enhanced tumor accumulation and greater anti-tumor efficacy than non-liposomal VNB.5

OBJECTIVES

1. To compare the anti-tumor activity of TLC178 with reference drug in human STS xenograft mouse models.
2. To investigate the pharmacokinetic and the drug distribution of VNB from a single intravenous (i.v.) injection of TLC178 or VNB in a tumor-bearing mouse model

MATERIALS AND METHODS

TLC178

TLC178 is a liposomal formulation of vinorelbine tartrate, a semi-synthetic vinca alkaloid. Vinorelbine tartrate has greater action on mitotic, rather than axon, microtubules, leading to a reduction in the neurotoxicity typically observed with this class of agents.6 A liposomal drug delivery system was developed for modulating PK profile and enhancing tumor localization of VNB, which results in attenuation of drug-related toxicities compared with non-encapsulated form.7

Study Designs for Pharmacodynamic and Pharmacokinetic (PK) Study (n ≥ 6)

Male C.B-17-SCID mice were subcutaneously inoculated with human sarcoma cell lines at the dorsal-lateral flank. Treatment was commenced once the sarcoma size reached the designed volume in average. Mice were randomly divided and i. x injected with test articles by groups. Tumor size and body weight were monitored every 2 to 3 days during the study. The therapeutic efficacy was evaluated in terms of tumor size, tumor growth delay (TGD), and tumor regression. A weight loss nadir of ≥20% of the initial body weight was considered toxic. Samples of plasma, skin, and tumor were collected from each mouse at the designated time point for the PK study, including 0.083, 1, 4, 6, 24, 48, and 72 hours post-dose.

RESULTS AND DISCUSSION

TLC178 showed improved anti-tumor activity without body weight loss in SJCRH30 human RMS and HT1080 human STS xenograft mouse models when compared with VNB alone or VNB in combination with CTX or DOX alone. (Figure 1, 2 and 3; Table 2)

TLC178 showed greater tumor accumulation in than in skin and plasma when compared with VNB (Figure 4).

REFERENCES