

ANTIPROTEOLYTIC THERAPY TARGETING UROKINASE-

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PLASMINOGEN ACTIVATOR FOR THE TREATMENT OF BREAST CANCER - A PHASE I STUDY



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Introduction

Distant metastases rather than the primary tumor itself remains the principle cause of death in patients with malignant solid tumors. There is abundant experimental evidence that the plasminogen activator system plays a key role in tumor invasion and metastasis. The serine protease urokinase-type plasminogen activator (uPA) and its inhibitor PAI-1 are involved in degradation of the tumor stroma, the extracellular matrix, and basement membrane. At this time uPA and PAI-1 are the only biomarkers that have been validated by the European Organization for the Treatment and Research of Cancer (EORTC) at the highest level of evidence (LOE I) with regard to their clinical utility in determining breast cancer prognosis. The serine protease inhibitor WX-UK1 inhibits uPA and other serine proteases (e.g. plasmin, thrombin, and trypsin).

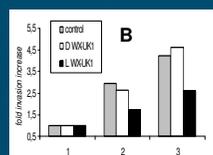
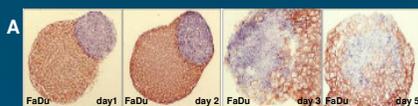
Objective and Summary

Under the Award, patients diagnosed with advanced solid tumors (phase I trial) and advanced breast cancer (phase II trial) will be administered with WX-UK1 in combination with capecitabine (Xeloda®, Roche). So far, a phase I trial of WX-UK1 in combination with capecitabine has been initiated at the Fox Chase Cancer Center (FCCC) after having obtained IND from the FDA and approval from the FCCC Institutional Review Board and Human Subject Research Review Board of the DoD. The goals of this phase I trial is to establish a MTD of WX-UK1 in combination with capecitabine. Both clinical trials will evaluate efficacy, safety and tolerability, pharmacodynamics, and pharmacokinetics of WX-UK1 in combination with capecitabine in breast cancer patients who have failed standard therapies. In particular, the phase II trial will examine whether if the combination treatment of WX-UK1 with capecitabine is synergistic and, hence, more effective in the therapy of breast cancer patients than capecitabine treatment alone.

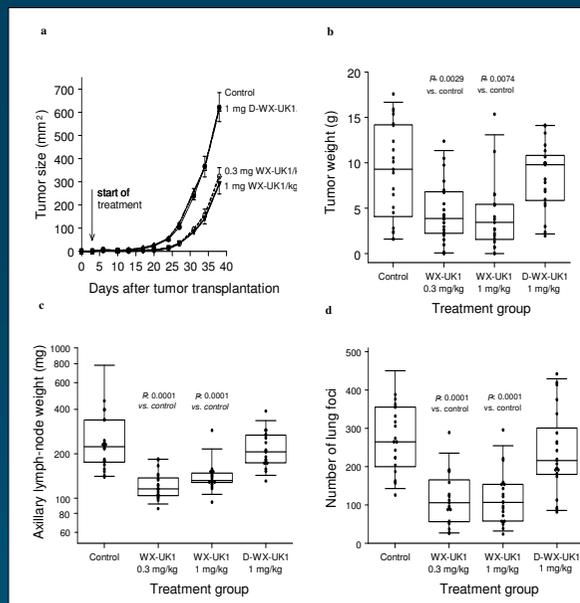
Preclinical background – Prevention of tumor cell invasion

in vitro data

A: Time course of FaDu cell invasion into co-cultured fibroblast spheroids.
B: Inhibition of FaDu cell invasion into co-cultured primary skin fibroblast spheroids at 1.0 µg/ml of WX-UK1 or 1.0 µg/ml of D-WX-UK1 relative to drug-free control over 3 days; the number of tumor cells invading the fibroblast core of the spheroid were determined. Each bar represents the mean of 2x8 spheroid analyses performed in two independent experiments.



in vivo efficacy data



Anti-tumor and anti-metastatic activity of WX-UK1 and the inactive D-enantiomer of WX-UK1 in rats bearing BN-472 breast tumors. Rats were treated by subcutaneous injections once a day for a period of 5 weeks. Treatment started 3 days after tumor inoculation. The rats of the control group received the vehicle (5% D-mannitol in water). The rats in the different treatment groups received two dosages of WX-UK1 (0.3 mg/kg or 1 mg/kg), or 1 mg/kg of the D-enantiomer of WX-UK1. Tumor size was measured twice a week to assess the kinetics of primary tumor growth (a), and the tumor weight (b), axillary lymph-node weight (c), and the number of lung foci (d), were determined after sacrificing the animals at the end of the experiment. (a) Primary tumor size is plotted as the mean ± standard error of the mean (●-●, vehicle control group; ▲-▲, 1 mg D-WX-UK1/kg; ○-○, 0.3 mg WX-UK1/kg; ▼-▼, 1 mg WX-UK1/kg). (b,c,d) Box-Whisker graphs, in which the boxes show the median, the 25th and 75th percentiles as horizontal lines, the whiskers indicate the 5th and 95th percentile ranges, and the dots represent all the individually observed values. Uncorrected P-values are given; when correcting for multiple comparisons, a P below 0.017 (critical level=0.05/3) indicates statistical significance when testing all treatment groups versus control. Reference: B. Han et al. Thromb Haemost. 2005 Apr;93(4):779-86

Phase I trial

Title

Phase I Study of the Antiproteolytic Targeting Therapy: Urokinase-Plasminogen Activator (uPA) Inhibitor WX-UK1 in Combination with Capecitabine in Advanced Malignancies

Primary Objectives

1. To determine the maximum tolerated dose (MTD) of four weekly infusions of WX-UK1 in combination with one 14-day cycle of capecitabine.
2. To define the dose-limiting toxicities of weekly WX-UK1 in combination with capecitabine.

Secondary Objectives

1. Safety and tolerability.
2. Pharmacokinetics of WX-UK1, capecitabine, and their principal metabolites in plasma; concentrations of WX-UK1, capecitabine, and their principal metabolite(s) in urine.
3. Determine potential effects of WX-UK1 on biomarkers, including levels of PAP, D-dimer, uPA/PAI-1-complexes and suPAR in plasma and suPAR and suPAR-D2D3 in urine.
4. Determine potential effects of WX-UK1 on tumor markers in blood.
5. Describe any preliminary evidence of antitumor activity of this combination.

Status

The patient enrolment of the first three dose cohorts of WX-UK1 (0.3/0.6/1.0 mg/kg) has been completed. In these cohorts no SAEs related to the investigational drug were reported and no relevant changes of safety parameters, safety laboratory, ECG and vital signs were seen. Furthermore, no change in the pharmacokinetics of capecitabine and WX-UK1 was observed.

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