A phase I study to evaluate safety, tolerability, pharmacokinetics and activity of Oraxol in patients with advanced malignancies.

Wen Wee Ma, Nilofur Saba Azad, Elaine Tat Lam, Jennifer Robinson Diamond, Grace K. Dy, Mateusz Opyrchal, Denise Gallagher, Caden Brennen, David Cutler, Douglas Kramer, Wing-Kai Chan, Rudolf Kwan, Gerald J. Fetterly, Alex A. Adjei, Antonio Jimeno
Mayo Clinic, Rochester, MN; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; University of Colorado, Aurora, CO; Roswell Park Cancer Institute, Buffalo, NY; Athenex Pharmaceuticals, Buffalo, NY

BACKGROUND

Oraxol is an oral formulation of paclitaxel (PTX) co-administered with the potent, selective and poorly absorbed P-glycoprotein inhibitor HM30181A (HM).

• HM enhances the GI absorption of PTX thereby improving PTX bioavailability following oral administration.
• Pharmacokinetic (PK) modeling of prior data showed that fixed dose administration was feasible.

OBJECTIVES

The primary objective of this study is to determine the maximum tolerated dose (MTD) in patients (pts) with advanced tumor.

The secondary objectives include determining the toxicity profile, safety and tolerability, PK profile of Oraxol, optimal dosing schedule of HM to enhance PTX absorption, and preliminary efficacy such as tumor response.

METHODS

• Pts with metastatic or unresectable solid tumor, ECOG PS 0 to 1 and adequate organs function were eligible.
• Prior PK modeling showed the feasibility of fixed dose administration orally.
• Pre-medication with steroids/anti-histamines were not required.
• The dose escalation utilized the standard 3+3 design to determine the MTD (Part 1), and then expanded to enroll additional pts at the MTD (Part 2). The treatment consisted of sequential administration of HM oral 15 mg then PTX oral 270 mg daily while fasting, and 2 sequences were evaluated:
  • Arm A: HM given once per dosing week (Day 1, 8 and 15)
  • Arm B: HM given prior to each PTX dosing

Dose escalation was achieved by increasing the number of consecutive dosing days (2-day, 3-day, 4-day and 5-day) per cycle x3 then 1 week rest, on an every-4-week cycle.

• Pts were monitored for dose limiting toxicity (DLT) during the first cycle for dose escalation/de-escalation decisions.
• Adverse events (AEs) were assessed and scored per NCI CTCAE v4.03; tumor response by RECIST v1.1.

RESULTS

• Plasma samples were obtained at pre-determined timepoints for PK evaluation.
  Samples were analyzed for PTX and HM30181A using a validated LC-MS/MS assay. The lower limit of quantitation was 0.5 and 1.0 ng/mL, respectively.

• A total of 34 pts received treatment and were evaluable for AEs.
  • Part 1: 24 were DLT evaluable and 1 DLT (febrile neutropenia) occurred at the 5-day dose level.
  • Part 2: 10 pts were enrolled and treated at the 5-day dose level.

• Safety: The most common (³30%) treatment-related AEs (TRAEs) were nausea, diarrhea, anorexia and vomiting.
  Serious TRAEs included febrile neutropenia, pneumonia and dehydration.
• No hypersensitivity reactions were observed.
• Efficacy: 2 partial responses were observed in salivary gland and ovarian cancers at the 5-day dose level.

CONCLUSIONS

• The maximum tolerated dose was not reached, and the highest dose level (HM plus PTX 270 mg daily x 5) was selected for expansion.
• No hypersensitivity reactions were observed and prophylactic steroid/anti-histamine was not needed.
• Sequential oral administration of a p-gp inhibitor and PTX achieved clinically efficacious PTX level, demonstrating evidence of anti-tumor activity.