Name:_____

M390: Principles of Pharmacotherapy in Clinical and Translational Cancer Research

Follow-up case study

Instructions: You are the principal investigator for a sponsored trial of a new investigational agent in diffuse large B-cell lymphoma (DLBCL) and are writing your trial protocol. Selected mock data and information from the Investigator's Brochure for the investigational drug you are studying are provided below.

Use these mock data to select the **best** answer to each of the multiple-choice questions that follow relating to your study design. Some of the mock data have been provided as distractors and may not be relevant to the questions. A score of 80% (8 out of 10 questions correct) is required for passing.

Contact Lane Nguyen, PharmD, BCPPS (nguyenl1@mskcc.org) with any questions regarding the assignment.

Investigator's Brochure

1 Physical, chemical, and pharmaceutical properties and formulation

1.1 Drug substance physicochemical properties

1.1.1 Nomenclature

International nonproprietary name: Ergoplixinib

United States adopted name: Ergoplixinib phosphate

IUPAC name: [redacted]

Chemical name: [redacted]

Chemical structure: [redacted]

Chemical Abstracts Service registry no.: 11827-A

Molecular formula (salt form, anhydrous): $C_{23}H_{26}N_7 \bullet H_3PO_4$

Other names: MSK578

1.1.2 Physicochemical properties

Appearance: yellowish powder

Solubility: Ergoplixinib phosphate is highly soluble in water and ethanol. In aqueous buffer ranging from pH 1.0 to 8.0, the drug product remained highly soluble.

1.2 Drug product pharmaceutical properties

1.2.1 Description and composition

The present available formulation of ergoplixinib phosphate is coated immediate-release tablets. These have been developed in 75mg, 150mg, 225mg, 300mg, and 375mg strengths for oral administration. All strengths are compressed into tablets from a common blend and are available globally.

In addition to ergoplixinib phosphate, the coated immediate-release tablets contain several excipients: copovidone, sodium stearyl fumarate, hydroxypropylcellulose, polysorbate 80, and calcium phosphate dibasic. The coating of the 75mg and 375mg tablets contains iron oxide yellow, talc, and titanium oxide. The coating of the 150mg tablets contains iron oxide red, talc, and titanium dioxide. The coating of the 225mg tablets contains iron oxide red, iron oxide yellow, talc, and titanium dioxide. The coating of the 300mg tablets contains iron oxide red, iron oxide black, talc, and titanium dioxide. The tablets are debossed on one side with the letter 'M'; the other side is debossed with '75' (for 75mg tablets), '150' (for 150mg tablets), '225' (for 225mg tablets), '300' (for 300mg tablets), or '375' (for 375mg tablets).

1.2.2 Storage conditions

Based on available stability data, the coated immediate release ergoplixinib phosphate tablets should be stored at room temperature: 20°C to 25°C. Excursions to 15°C to 30°C are permissible.

1.3 Hazards and precautions

No specific hazards have been identified. Exercise appropriate hygiene and clinical practice precautions such as thorough handwashing before and after handling ergoplixinib phosphate tablets.

2 Non-clinical studies

2.1 Nonclinical pharmacology

2.1.1 Primary pharmacodynamics

Intracellular Enzyme X has been implicated in the pathogenesis of approximately one-third of cases of diffuse large B-cell lymphoma (DLBCL) due to overexpression induced by Mutation Y in *Gene X*. In *in vitro* studies, ergoplixinib showed potent, irreversible binding of Enzyme X in DLBCL cell lines overexpressing Enzyme X, with half-maximal inhibitory concentrations (IC50) < 5nM. Exposure to ergoplixinib led to dose-dependent apoptosis in Enzyme X-overexpressing DLBCL cell lines, with minimal activity in cell lines not overexpressing Enzyme X across concentrations.

In *in vivo* studies, ergoplixinib demonstrated dose-dependent antitumor activity in Enzyme X-overexpressing murine DLBCL xenograft models. Administration of ergoplixinib by intraperitoneal injection and oral gavage produced significantly increased survival in xenografts compared to vehicle-treated mice.

Overexpression of Enzyme X in certain solid tumors has also been demonstrated in preclinical models. Mice implanted with patient-derived colorectal tumors overexpressing Enzyme X demonstrated reduction in tumor growth at levels similar to 5-fluorouracil.

2.1.2 Secondary pharmacodynamics

In mouse Enzyme X-overexpressing DLBCL xenograft models, oral administration of ergoplixinib produced significant tumor reduction and normalization of tissue histology. High-throughput cellular thermal shift in vitro assays with mass spectrometry indicated ergoplixinib binding to Enzyme X is highly specific, with no identified off-target enzyme binding at concentrations up to 500nM.

2.2 Nonclinical pharmacokinetics

2.2.1 Bioanalytical methods

Ergoplixinib concentrations are measured in plasma using a validated liquid chromatography-tandem mass spectrometry method.

2.2.2 Absorption

Caco-2 cell experiments suggested high intestinal permeability of ergoplixinib across a wide range of concentrations. [^{14}C]-radiolabeled ergoplixinib disposition studies in mice, rabbits, dogs, and cynomolgus monkeys indicated oral bioavailability ranging from 60% to 90%. Ergoplixinib showed stability in gastrointestinal fluids of multiple species.

2.2.3 Distribution

In [^{14}C]-ergoplixinib disposition studies, ex vivo measured plasma protein binding ranged from 30% to 60% across animal species. Drug-derived radioactivity indicated broad tissue distribution in mice administered [^{14}C]-ergoplixinib by oral gavage, with the highest concentrations noted in gastrointestinal tract, liver, bile, and skin. Minimal drug-derived radioactivity was identified in the brain and cerebrospinal fluid.

2.2.4 Metabolism

In pooled human liver microsome assays, ergoplixinib was primarily eliminated by oxidative metabolism to the major hydroxylated metabolite M2 and several minor hydroxylated metabolites. Glucuronide conjugates of the major metabolite M2 were identified. The major metabolite M2 and its subsequent glucuronide conjugate were formed by dogs. The M2 metabolite demonstrated pharmacologic activity against Enzyme X at approximately one-half of the activity of parent drug. The glucuronidated M2 metabolite demonstrated no appreciable pharmacologic activity against Enzyme X.

Oxidative metabolism of ergoplixinib was predominantly catalyzed by cytochrome P450 (CYP) 3A4, with minor metabolic activity by CYP2D6. Ergoplixinib did not inhibit CYP1A2, CYP2A6, CYP3A4, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 at concentrations ranging from 5nM to 1000nM. There was no indication that ergoplixinib induces expression or activity of CYP enzymes across a broad concentration range. The major metabolite M2 was predominantly eliminated via glucuronidation by UDP-glucuronosyltransferase (UGT) 1A1. M2 did not appear to inhibit or induce CYP enzymes at the concentrations produced during microsome assays.

After the major metabolite M2 was identified as a substrate of UGT1A1, ergoplixinib metabolism was evaluated in assays using human liver microsomes from donors homozygous for UGT1A1*28. The mean concentration of the glucuronidated M2 metabolite produced by UGT1A1*28 homozygous liver microsomes was 92% lower than the mean concentration produced by liver microsomes from pooled donors.

In vitro drug transporter studies have not been performed.

2.2.5 Excretion

In dogs, most [^{14}C]-ergoplixinib drug-derived radioactivity was detected in feces and bile (65% of dose). Approximately 30% of radioactivity was identified in urine, almost exclusively as the glucuronidated form of the M2 metabolite. In lactating rats, drug-derived radioactivity was not detected in milk.

3 Human studies

3.1 Pharmacokinetics, metabolism, and pharmacodynamics in humans

Ergoplixinib has been evaluated in healthy subjects in single- and multiple-dose studies, a food effect study, and mass balance studies. Ergoplixinib has also been evaluated in a phase I trial of patients with solid tumors overexpressing Enzyme X. Formal drug-drug interaction studies have not been conducted in humans.

3.1.1 Absorption and distribution

In healthy subjects administered single doses of [^{14}C]-ergoplixinib while fasting, oral absorption was rapid and bioavailability was approximately 90%. Maximum plasma concentration (Cmax) was reached approximately 1 hour post-dose. Cmax and area under the curve (AUC) increased proportionally with single doses ranging from 50mg to 500mg. When administered with a high-fat meal, mean Cmax was decreased by 25% and mean time to Cmax was delayed to 6 hours post-dose; AUC was significantly reduced by over 50% compared to fasting administration.

In healthy subjects and patients with solid tumors administered multiple doses of ergoplixinib, the mean volume of distribution at steady state was approximately 8000 liters. Across dose ranges, the fraction of unbound ergoplixinib was approximately 2%, with most drug bound to albumin. Concentration-time profiles indicated two-compartment distribution, with a rapid distribution phase.

3.1.2 Metabolism

In humans, the majority of circulating drug-related material identified in plasma throughout sampling was unchanged parent drug. One major hydroxylated metabolite, M2, was identified in the plasma of healthy subjects, representing 30% of parent drug AUC, with pharmacologic activity approximately half that of the parent drug based on in vitro data. While in vitro data indicated CYP3A4 to be the primary enzyme involved in metabolism of ergoplixinib, no human drug-drug interaction studies have been performed.

3.1.3 Excretion/elimination

In healthy subjects administered single doses of [^{14}C]-ergoplixinib, approximately 56% of radioactivity was excreted in the feces, primarily as unchanged parent drug. Approximately 20% of radioactivity was excreted in the urine, almost exclusively as the inactive glucuronidated form of the M2 metabolite. In healthy subjects and patients with solid tumors administered multiple doses, concentration-time profiles indicated first-order elimination pharmacokinetics. The mean terminal elimination half-life of parent drug was approximately 12 hours; the mean elimination half-life of the active M2 metabolite was approximately 3 hours.

3.2 Pharmacokinetics in special populations

3.2.1 Renal impairment

In patients with mild-to-severe renal impairment, single doses produced similar pharmacokinetic profiles of ergoplixinib. However, the AUC and half-life of the M2 metabolite was significantly prolonged in patients with moderate-to-severe renal impairment. Based on in vitro activity of the M2 metabolite and increases in mean AUC in patients with renal dysfunction, the pharmacological activity of parent ergoplixinib and M2 in patients with moderate-to-severe renal impairment is estimated to be up to 1.5-fold that of patients with normal renal function or mild renal impairment. Based on these results, it is recommended that the starting dose of ergoplixinib be reduced by at least 50% in patients with creatinine clearance less than 30mL/min. It is unknown if ergoplixinib is dialyzable, although its high serum protein binding in healthy subjects suggests low likelihood.

3.2.2 Hepatic impairment

In patients with mild, moderate, and severe hepatic impairment according to Child-Pugh scores, mean ergoplixinib AUC was increased by 94%, 53%, and 55%, respectively. Mean AUC of the M2 metabolite was increased by 23%, 40%, and 35% in patients with mild, moderate, and severe hepatic impairment, respectively. These data suggest no clear relationship between degree of hepatic impairment according to Child-Pugh score and drug exposure, but indicate that any degree of hepatic impairment may significantly increase exposure to ergoplixinib. Therefore, it is recommended that patients with hepatic impairment have starting dose of ergoplixinib reduced by at least 50%.