the N-terminal region of ASK-1. When activated in response to various cytotoxic stresses (e.g. H_2O_2, TNF-α, UV light, heat shock) ASK-1, a MAPKKK, can activate both the c-Jun N-terminal kinase (JNK) and p38 MAP kinase pathways leading to a variety of cellular responses including apoptosis. Immunoprecipitation of Trx from lysates of control or treated HCT116 cells has shown that PMX 464 triggers dissociation of ASK-1 from Trx. Futhermore, by using antibodies specific for their phophorylated forms, JNK and P38 activation, are observed.
In order to investigate *in vitro* binding of cellular proteins, a carboxylate analog was immobilized to a solid media leading to identification of peroxiredoxin (Prx) as a molecular target. Prxs act as antioxidants and also regulate H_2O_2-mediated signal transduction, possessing a strictly conserved catalytic cysteine-SH (thiol). Overexpresion of Prx, detected in several cancers correlates with resistance to apoptosis induced by radiation or cisplatin.
In conclusion, perturbation of events downstream of Trx inhibition by PMX 464 has been detected. PMX 464 is not an indiscriminate thiol inhibitor, however, additional molecular targets such as Prx, involved in redox regulation have been identified.

432 POSTER

Phase I study of Amplimexon™ (imexon, inj.) in patients with advanced solid tumors and lymphomas: final report

T. Dragovich[1], M. Mendelson[2], M. Modiano[3], M. Gordon[2], K. Grenier[4], R. Dorr[4], E. Hersh[4]. *[1]University of Arizona, Arizona Cancer Center, Tucson, USA; [2]Premiere Oncology, Scottsdale, USA; [3]Arizona Oncology Associates, Tucson, USA; [4]Amplimed Corp., Tucson, USA*

Background: Amplimexon (AMP) is an iminopyrrolidone agent, which causes cancer cell kill by inducing mitochondrial injury, cytochrome C leakage and apoptosis. We report here the final results from the phase I trial of Amplimexon in patients with advanced solid tumors and lymphomas.
Methods: The purpose of this trial was to establish safety and maximally tolerated dose of AMP and to investigate pharmacokinetic (PK) and pharmacodynamic (PD) parameters on this schedule. AMP was administered as a 30 min IV infusion, daily X 5, every 14 days. The dose was escalated from 20 up to 1000 mg/m^2.
Results: A total of 49 patients were treated. The MTD was established as 875 mg/m^2 dose. Dose limiting toxicities at 1000 mg/m^2 included grade 3 abdominal pain and grade 4 neutropenia. Common grade 1–2 toxicities included constipation, nausea, fatigue, anemia and anorexia. The systemic clearance of AMP averaged 160mL/min/m^2 at the MTD of 875 mg/m^2. The plasma half life was 95 minutes and the Cmax was 53 ug/mL. This yielded an AUC of 5517 min ug/mL and a Vd ss of 19.1 L/m^2. There were no differences in clearance on day 1 versus day 5, and for the different dose levels of imexon. Pharmacodynamic studies showed that plasma cystine, the Cys-Cys dimer, decreased in a dose-dependant fashion at doses $\geqslant$750 mg/m^2, with a 30% decrease noted 8 hours after the 875 mg/m^2 infusion ended. Other plasma thiols were unchanged by AMP. A patient with a refractory follicular Non-Hodgkin lymphoma achieved a partial response and 10 patients with other solid tumors achieved stable disease for >3 months.
Conclusions: AMP could be safely administered at 875 mg/m^2/d dose and has demonstrated encouraging antitumor activity in this phase I study. Phase II studies of AMP in patients with both epithelial and lymphoid malignancies are warranted.

433 POSTER

A population pharmacokinetic/pharmacodynamic model for the hematological effects of BI 2536 in cancer patients

D. Trommeshauser[1], I. Troconiz[2], C. Tillmann[1], A. Staab[1], G. Munzert[3]. *[1]Boehringer Ingelheim GmbH&Co KG, Department of Drug Metabolism and Pharmacokinetics, Biberach (Riss), Germany; [2]University of Navarra, Department of Pharmacy; School of Pharmacy, Pamplona, Spain; [3]Boehringer Ingelheim GmbH&Co KG, Department of Clinical Research, Biberach (Riss), Germany*

Background: Myelosuppression is usually one of the principal dose-limiting toxicities observed in patients treated with anticancer drugs. In this context, the population pharmacokinetic/pharmacodynamic (PK/PD) modelling approach has been shown to be an excellent tool to explore the drug response behaviour under a variety of dosing regimens, making the dose selection process less empirical. BI 2536 is a novel highly potent and specific inhibitor of the serine-threonine Polo-like kinase 1 (Plk1), a key regulator of cell cycle progression. Neutropenia as a mechanism-related toxicity indicates target inhibition in vivo and was the dose limiting toxicity observed in advanced cancer patients. The objective of the population pharmacokinetic/pharmacodynamic analysis was to develop a model that describes the haematological effects of BI 2536 and can serve as a tool to predict the influence of dose and schedule on hematotoxicity.
Methods: BI 2536 was administered as a 60 min intravenous infusion on day 1 of a 21 day treatment cycle (Dose levels 25–250 mg). Blood samples to determine the drug plasma concentration and the neutrophil count were taken at different time points during the 21 day treatment cycle. A semi-mechanistic model of chemotherapy-induced myelosupression (Friberg et al. J Clin Oncol 2002; 20: 4713−21) was used to describe the data. The analysis was performed using NONMEM, version V.
Results: BI 2536 BS plasma concentrations could best be described by a linear three compartment model. A moderate interindividual variability was established on clearance.
The neutrophil counts were adequately described using the semi-mechanistic model. This model allows the discrimination between system and drug related parameters. The estimates of the system related parameters obtained during analysis were similar to those reported previously for other compounds (Friberg et al).
Conclusion: The pharmacokinetics of BI 2536 were best described using a linear three compartment pharmacokinetic model. The time course of the hematological toxicity induced by BI 2536 and measured by the neutrophil cell counts was adequately described using a semi-mechanistic model developed and recently published (Friberg et al). The model developed will serve as a tool to predict hematologic side effects of further dosing schedules of BI 2536 given as a single agent or in combination with other modalities.

434 POSTER

Preclinical pharmacokinetic and comparative biodistribution studies of PX-866, a broad spectrum phosphatidylinositol-3-kinase (PI-3K) inhibitor, in F344 rats

K. Culotta[1], D. Kirkpatrick[2], J. Covey[3], C. Schultz[4], D. Mack[1], R. Rhea[4], T. Allen[1], G. Powis[4], M. Johansen[4], T. Madden[4]. *[1]UT M.D. Anderson Cancer Center, Pharmacy, Houston, USA; [2]ProlX Pharmaceuticals Corp, Tucson, USA; [3]NCI, DTP, Rockville, USA; [4]UT M.D. Anderson Cancer Center, Experimental Therapeutics, Houston, USA*

PX-866, a semisynthetic inhibitor of PI-3K, has antitumor activity as a single agent and in combination with inhibitors of EGF and VEGF signal transduction, and is in late stage pre-clinical development. Constitutive PI-3K activity is found in small cell lung cancer and in 40% of ovarian, head and neck, urinary tract, and cervical cancers. PX-866 is the result of a nucleophilic modification of the furan ring in wortmannin, conferring chemical stability and reduced toxicity. We investigated the plasma pharmacokinetics and tissue distribution in F344 rats following a large single dose of 12.5 mg/kg given IV or PO (0.5 mL of 4 mg/mL PX-866 in NS:DMA, 80:20, v:v). Following sacrifice, plasma and tissue samples were collected (5 animals/timepoint) over a span of 5 minutes to 72 hours following drug administration and immediately processed for analysis. PX-866 was extracted from plasma and tissues using either protein precipitation or tissue disruption followed by liquid-liquid extraction. Samples were quantified using LC/MS/MS in ESI+ mode (LLOQ = 0.1 ng/mL). PK parameters for PX-866 were determined fitting both two-compartment ($r^2 > 0.99$) and non-compartmental ($r^2 = 0.88$) models to the mean measured plasma concentration vs. time data. PX-866 given IV rapidly distributed with a peak plasma concentration of 12.1 ug/mL at 5 minutes and could be measured to 4 hours. Tissue distribution of PX-866 IV bolus was rapid and significant, achieving concentrations 4 times greater than concurrently measured in the plasma in highly perfused organs over the first 30 minutes following injection. IV PK parameters C_{max}, AUC, V_d, Cl, $t_{1/2}$, and MRT were 12.1 ug/mL, 1166.4 ng hr/mL, 3.2 L/kg, 10.7 L/hr/kg, 0.27 hrs, and 0.29 hrs, compared to PO values of 81.7 ng/mL, 19.2 ng hr/mL, 146.4 L/kg, 636.1 L/hr/kg, 0.16 hrs, and 0.25 hrs, respectively. Oral bioavailability of parent PX-866 was 1.64%, similar to the previously reported value of 1.05% in mice. In conclusion, PX-866 biodistribution is extensive, with rapid clearance from plasma and most major organs in F344 rats following 12.5 mg/kg IV bolus delivery. Further investigations of single and multiple dose of PX-866 in these and other species will be conducted to ascertain the drugs behavior in both rodent and non-rodent species.

435 POSTER

Modulation of the activity of tumour associated carbonic anhydrases for therapeutic benefit

L. Glassbrook, R. Wang, K. Williams, M. Jaffar, I.J. Stratford. *University of Manchester, School of Pharmacy, Manchester, United Kingdom*

Carbonic anhydrases (CAs) are metalloenzymes involved in the reversible hydration of carbon dioxide to bicarbonate and various physiological