mechanistic profile, which is different from that of DOX: BRN is a more potent topoisomerase II inhibitor that blocks the transcriptional activity of HIF-1a and circumvents ABC transporter-mediated efflux. Our data indicate that BRN is a potentially useful agent against diffuse large B cell lymphoma. Most importantly, its unique high CNS uptake makes BRN a good candidate for clinical evaluation in patients with diffuse large B cell lymphomas in CNS.

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Eribulin and cytochrome P450 effectors: *in vitro* studies and population pharmacokinetic–pharmacodynamic analysis

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Background: Eribulin belongs to the halichondrin class of antineoplastic agents and inhibits microtubule dynamics by suppressing microtubule growth without affecting shortening. Eribulin also sequesters tubulin into non-functional aggregates. The cytochrome p450 isoform, CYP3A4, has been shown to be the major enzyme responsible for eribulin metabolism in the liver. Here we report the results of *in vitro* studies and clinical population PK analysis of the effects of CYP P450 inhibitors and inducers on eribulin exposure as well as the effect of eribulin on co-administered drugs metabolized via CYP3A4 pathway.
Methods: The *in vitro* analysis utilized cultured primary human hepatocytes, isolated human liver microsomes, and cDNA-expressed recombinant CYP3A4 protein. Eribulin mesylate treatments of concentrations up to 10 μmol/L and exposure times ranging from 15 minutes to 3 days were used. Enzyme activity was measured by the specific CYP3A4-mediated hydroxylation of metabolites. Protein expression was determined immunocytochemically, and the nature of CYP3A4 inhibition by eribulin was determined by nifedipine dehydration. The population PK model was developed based on robust PK data collected from 7 phase I studies and sparse PK data collected from a phase II study. The model was constructed and evaluated from a final database consisting of 2729 observations from a total of 269 subjects. The effects of CYP3A4 inhibitors and inducers on eribulin clearance were tested as covariates in the population PK model.
Results: Eribulin inhibited CYP3A4 activity with an apparent inhibition constant (K_i) value ranging from 3 to 30 μmol/L (2190–21900 ng/mL, calculated as eribulin free base); this inhibition was shown to be reversible and competitive. In human hepatocytes, eribulin displayed minimal inhibition of carbamazepine, diazepam, paclitaxel, tamoxifen, midazolam, and terfenadine metabolism, at concentrations up to 10 μmol/L (7300 ng/mL). *In vitro* results were confirmed by population PK analyses that demonstrated co-administration of certain CYP3A4 inducers and inhibitors had no significant effect on eribulin clearance and exposure in clinical studies.
Conclusions: Eribulin, at clinically relevant concentrations (i.e. $\leqslant$700 ng/mL), has no effect on CYP3A4 expression, induction, enzyme activity or the processing of compounds metabolized by CYP3A4 *in vitro*. Clinical findings have confirmed that eribulin can be co-administered with drugs metabolized by CYP3A4.

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Eribulin mesylate pharmacokinetics in patients with solid tumors receiving repeated oral ketoconazole (KET)

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Background: Eribulin mesylate is a non-taxane microtubule dynamics inhibitor with a novel mechanism of action in development for the treatment of metastatic breast cancer, and other solid tumors. This study investigated the effects of ketaconazole (KET), a CYP3A4 inhibitor, on eribulin pharmacokinetics (PK).
Methods: In this phase I, randomized, open-label, 2-way crossover study, 12 patients with solid tumors were assigned to one of two groups. Group 1 (n = 6) received 1.4 mg/m^2 eribulin mesylate as a 2−5 min IV injection on day 1, 0.7 mg/m^2 eribulin mesylate IV + 200 mg oral KET on day 15, and 200 mg oral KET on day 16. Group 2 (n = 6) received 0.7 mg/m^2 eribulin mesylate IV + 200 mg oral KET on day 1, 200 mg oral KET on day 2, and 1.4 mg/m^2 eribulin mesylate IV on day 15. Plasma samples for PK analysis were collected over 144 hours post dose on days 1 and 15 of cycle 1. Log-transformed, dose normalized AUC and C_{max} values were analyzed using analysis of variance. Comparisons were made between eribulin alone and eribulin + KET treatment groups for AUC_∞ and C_{max}. Safety was also assessed.
Results: The C_{max} for eribulin + KET was not statistically different from that for eribulin alone (ratio of geometric least square means: 0.97, 90% CI 0.83, 1.12). Eribulin exposure (AUC_∞) following administration alone was statistically not different from that of eribulin + KET (ratio of geometric least square means: 0.95, 90% CI 0.80, 1.12). KET had no apparent effect on eribulin clearance (CL) or elimination half-life ($T_{1/2}$). CL (mean, [SD]) was 3.10 (1.903) for eribulin and 3.37 (2.507) L/hr for eribulin+KET. $T_{1/2}$ was 45.6 (13.62) vs 40.5 (7.69) hr, respectively. The most frequent treatment-related adverse events (AEs) reported for eribulin were nausea, fatigue and neutropenia, each occurring in 4 patients. For eribulin + KET, the most frequent AEs were nausea (n = 3) and fatigue (n = 3). Low numbers preclude the drawing of conclusions from comparisons across treatment groups, although the incidence and severity of AEs were broadly similar. There were no deaths, life threatening serious AEs or serious AEs reported as treatment related.
Conclusions: Co-administration of KET had no statistically significant effect on single dose exposure to eribulin. Eribulin was generally safe and well tolerated.

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ALB 109564(a), a novel tubulin inhibitor: phase 1 trial in patients with solid tumours

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Background: ALB 109564(a) [ALB] is a novel antimitotic agent which functions as a tubulin inhibitor, interfering with microtubule polymerization resulting in metaphase arrest. ALB showed significantly greater activity compared to vinorelbine in a number of xenograft models (NSCLC [H460], SCLC [H69], colon [Colo205] and prostate [PC3]); these data demonstrate that ALB has a preclinical profile that is superior to that of this established vinca alkaloid anti-cancer agent and warranted clinical development.
Methods: This study sought to determine the maximum tolerated dose based upon first cycle toxicity in 3−6 patients at each dose level, as well as to evaluate the pharmacokinetics of ALB when administered intravenously once every three weeks. The starting dose was 1.2 mg/m^2, and dose escalation by cohort proceeded according to a modified Fibonacci scheme.
Results: 35 patients have been administered ALB across 10 dose levels (1.2 to 22.5 mg/m^2). No dose-limiting toxicities have been observed. Adverse events reported to be at least possibly related to study drug were constipation (n = 12), fatigue (n = 5), anemia (n = 3), diarrhea (n = 3) blurred vision (n = 2), paresthesia (n = 2), peripheral neuropathy (n = 2), and neutropenia (n = 1). With the exception of neutropenia (grade 3), all adverse events were either grade 1 or 2. The mean half-life of ALB is 18.54±8.28 hours, which is comparable to that of approved vinca alkaloids. Of 28 patients evaluable for clinical activity, one alveolar soft part sarcoma (ASPS) patient, who had marked progression prior to enrollment, has received 26 cycles of study drug with stable disease. An additional seven patients have had stable disease after two or more cycles; one anal carcinoma (13 cycles), one pancreatic carcinoma (7 cycles), two colon carcinomas (4 and 2 cycles), one NSCLC (4 cycles), one leiomyosarcoma (3 cycles), and one neuroendocrine tumor (2 cycles).
Conclusions: ALB is well tolerated, with a favorable pharmacokinetic profile, and has shown preliminary activity in disease types not typically treated with vinca alkaloids. Further trials in soft tissue sarcoma are in development.