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A phase I dose escalation and pharmacokinetic study of the novel mitotic checkpoint inhibitor GSK923295A in patients with solid tumors

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Background: The mitotic spindle assembly checkpoint is the major cell cycle mechanism for maintaining genomic stability. Centromere-associated protein E (CENP-E) plays a critical role in maintaining and silencing mitotic checkpoint signaling. CENP-E mRNA is overexpressed in a variety of human tumors relative to adjacent normal tissue suggesting that it may have an important role in tumor cell proliferation. GSK923295A is a potent and selective small molecule inhibitor of CENP-E with broad activity against solid tumor and hematologic cancer cells in vitro and in murine tumor xenograft models. The purpose of this study is to determine the maximally tolerated dose (MTD), dose-limiting toxicities (DLTs), pharmacokinetics (PK), and pharmacodynamics of GSK923295A in patients with advanced solid tumors.
Methods: GSK923295A is administered by a 1-hour intravenous infusion on Days 1, 8, and 15 of 28-day treatment cycles to adult patients with refractory advanced solid tumors. An accelerated titration scheme (two pts per cohort) with transition to a standard (40% or 33%) dose escalation scheme is planned if two grade 2 toxicities or one DLT are observed in the first treatment cycle. Blood samples for GSK923295A PK analysis are collected on Days 1 and 15 over a 48 hour period. Pre- and post-treatment FDG-PET and tumor biopsies are performed in selected patients.
Results: Eleven patients (median age 55 years, cancers of pancreas (n = 3), colon (3), lung (2), stomach (1), parotid gland (1), and liver (1)) have been treated at 10 (n = 2), 20 (2), 40 (2), and 80 mg/m^2 (5). Safety and PK data are available for eight and nine subjects respectively. One DLT (reversible grade 3 AST elevation) was reported at 80 mg/m^2 and this dose level has been expanded to six pts. The most frequent adverse events (AEs) have been nausea (50%), abdominal pain (38%), anorexia (38%), and fatigue (38%) with the majority of AEs being grade 1 (69%) or grade 2 (29%) with no grade 4 AEs. Best responses to date include two patients with stable disease (hepatoma, 6 months and pancreatic cancer, 3+ months). Median (range) systemic clearance and elimination half-life of GSK923295A are 16 L/h/m^2 (5.5–27) and 9.0 h (2.7–21) respectively with minimal intrapatient PK variability observed to date.
Conclusion: GSK923295A is well tolerated at the dose levels evaluated to date with no neurotoxicity reported. Dose escalation to MTD will continue as described.

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Phase I, pharmacokinetic (PK), dose-escalation study of EZN-2968, a novel hypoxia-inducible factor-1 alpha (HIF-1a) antagonist, administered weekly in patients (pts) with solid tumours

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Background: HIF-1 is a transcription factor that regulates >100 genes important in tumor metabolism, pH, neovascularization, drug resistance, invasion, autophagy, and cell survival. Increased HIF-1a levels are associated with poor prognosis in several neoplasms. Down-regulation of HIF-1a may have broad therapeutic application. This study is being conducted to determine the safety, tolerability, PK, maximum tolerated dose, recommended dose, and preliminary evidence of antitumor activity of EZN-2968, a locked nucleic acid (LNA) RNA antagonist that specifically inhibits the expression of HIF-1a.
Methods: Pts with advanced solid tumors were enrolled and treated with EZN-2968 administered as a 2-hour IV infusion wkly x 3 q 6 wks using a 3+3 escalating-dose design. Dose escalation was based on drug-related toxicities observed during the first cycle.
Results: 12 pts (6 females, 6 males; median age = 56 years [range = 37–87 years]) were treated with EZN-2968 doses of 1.0 (4 pts), 1.5 (3 pts), 2.0 (1 pt), 2.3 (3 pts), and 3.5 (1 pt) mg/kg/dose. Tumor types included colorectal cancer (6 pts), sarcomas (2 pts); clear cell renal cancer (CCRC) (1 pt), hepatocellular carcinoma (HCC) (1 pt), laryngeal adenocystic cancer (LAC) (1 pt), and pancreatic cancer (1 pt). No dose-limiting toxicities were observed. No drug-related Grade 3 or 4 adverse events were reported. Plasma PK in first 3 cohorts (10 pts) indicated that clearance and t1/2 appear to be dose independent, suggesting linearity of PK across the dose levels (see Table). Exposure to EZN-2968, as measured by AUC, increased with dose, but in a manner that was less than dose proportional. Prolonged stable disease (RECIST) with modest reduction in tumor size was observed in 1 pt with CCRC (13 months+, 15% tumor reduction) and 1 pt with HCC (6 months+, 14% tumor reduction). Both of these patients had progressed on prior anti-VEGF treatments.
Conclusions: EZN-2968 was well tolerated in previously treated pts with solid tumors. PK data support weekly administration of EZN-2968. Antitumor activity was observed in pts with CCRC and HCC. Dose escalation is ongoing, and final results will be presented at the meeting.

Dose (mg/kg)	N	C_{max} (ng/mL)	AUC(0-t) (h·ng/mL)	t1/2 (h)
1.0	4	4598±2439	5954±2680	0.74±0.46
1.5	3	4883±3049	7719±4769	1.02±0.44
2.0	1	7573	10492	0.85
2.3	2	6296±2641	8700±3834	0.82±0.04

Mean values±standard deviation are reported.
For AUC(0-t), t = time of last measurable concentration.

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A Phase 1 dose-escalation, pharmacokinetic (PK) and pharmacodynamic (PD) evaluation of intravenous LY2275796 (LY), an eIF-4E antisense oligonucleotide (ASO) in patients with advanced solid tumors

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Overexpression of eIF-4E protein has been documented in multiple human tumors including head and neck, prostate, and lung (Ruggero et al. 2004). LY is a 20-mer 2'-O-methoxyethyl-gapmer second-generation (ASO) that specifically binds to eIF-4E mRNA, leading to degradation of the eIF-4E message and subsequent inhibition of eIF-4E protein expression. In preclinical studies with LY, administration of LY to tumor bearing mice results in reduced eIF-4E message and protein, as well as inhibition of tumor growth. The 'JKAF' trial is a Phase I dose escalation trial in patients with advanced solid tumors for whom no curative options exist and have exhausted the standard palliative options. JKAF is designed as a three-part study; Part 1 single patient cohorts, Part 2 three patient cohorts with biopsies and Part 3, dose expansion cohort with biopsies. Extensive PK collection is integrated into all stages of this study. LY is administered IV as a flat dose with three loading doses being administered 24 hours apart on days 1, 2 and 3 in order to achieve a steady state concentration of the drug in the tissues. Weekly doses are then administered as maintenance. To date 17 patients have been treated. Twelve patients completed the 28 day period required for inclusion in evaluation of tolerability of LY. Five patients progressed in the first 28 days and had to be replaced.
In part 1 of the study doses of 100, 200, 400 and 600 mg were explored. In part 2 of the study doses of 800, 1000 and 1200 mg were explored. Part 3 has not yet opened. The drug is well tolerated at all dose levels, and to date no dose limiting toxicities have been observed. The median number of cycles administered is two. The most commonly observed drug-related grade 1−2 adverse events are fatigue, nausea, anorexia and increases in activated partial thromboplastin time (aPTT). The increases in aPTT are likely an ASO class effect and are transient and resolve within 24 hours of drug administration without any accompanying bleeding episodes. Furthermore there have been no reports of hemorrhage at doses up to 1200 mg. The PK of the drug (as measured in the serum) have been relatively dose linear at doses up to 1000 mg. Preliminary analysis of the biopsies from Part 2 of the study suggest that there is a reduction in the eIF-4E message at dose levels of 800 mg and 1000 mg, however the signal does not seem to increase significantly between 800 mg and 1000 mg.