Background

HIF-1 is a critical mediator of adaptive responses to changes in tissue oxygenation.1,2 In cancer cells, HIF-1 levels increase in response to various stimuli and are regulated by the stability, ubiquitination, and degradation of HIF-1α.3 In addition to intratumoral hypoxia, multiple other mechanisms may result in increased levels of HIF-1α in cancer cells.4 Examples of such mechanisms include abnormalities in signaling via the phosphorylated (ERK) 5/6-MKK7-ATM (neutrophil) signal (3G) and IGFR-1 (IGF), which are alterations that can result in HIF-1α stabilization.5 HIF-1α stabilizes the vascular endothelial growth factor (VEGF) and the hypoxia inducible factor 2 (HIF-2).6,7 HIF-1α stabilizes VEGF and HIF-2α, which activate the PI3K and Akt signaling pathways, leading to the activation of the Akt-PKB and PKC pathways.8,9

Clinical Study

Study Design

- Schedule of administration
  - Original: Five daily 2-hour intravenous infusions per 4-week cycle
  - Amendment: Three-weekly administration, with two doses the first week

Objectives

- Determine maximum tolerated dose
- Determine recommended Phase 2 dose
- Determine PK profile
- Determine pharmacokinetic parameters; relevant laboratory parameters, functional parameters, and safety
- Detect potential evidence of anti-tumor activity

Key Eligibility Criteria

- Advanced or metastatic solid tumor or lymphoma; refractory to standard therapy
- Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2
- Prothrombin time (PT), partial thromboplastin time (PTT), International Normalized Ratio (INR), serum creatinine, and total bilirubin ≤1.5 x upper limit of normal (ULN)
- Asparaginase aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x ULN

Methods

- Plasma concentrations of EZN-2968 determined by ELISA assay method
- Dose proportionality determined with linear regression between dose and area under the drug concentration-time curve (AUC)
- PK parameters
- Infinitely weighted using nonlinear model
- In-depth analysis performed using model component with population-based approach, with inclusion of prior specific biologic variables
- Analysis using NONMEM Version VI.2

Results

Patient and Treatment Information

At the time of the cut-off date, 26 patients had been enrolled and treated. Three patients were still being treated at the time of the cut-off date. Two of the 23 patients, for whom the data were curtailed at day 28 (cycle 1), had a basal AUC(28) (calculated by area of time) considered unlikely related to study drug, and withdrawn from the study. The median age of the treated patients was 60 years (range: 40-79; Table 1). Of the 23 patients, 13 (53%) were men, 11 (47%) were women, and 10 (44%) were white. EZN-2968 performance status was 1 for 9 patients (41%), 2 for 13 patients (56%), and 2 for 2 patients (8%). All patients had received prior chemotherapy. The median number of prior treatments was 2 and 3 for colorectal cancer (CRC) and renal cancer, respectively. Tumor types included colorectal cancer (CRC) (10 patients), renal cell cancer (RCC) (5 patients), soft tissue sarcoma (STS) and ovarian cancer (3 patients each); and breast cancer, endometrial, and prostate cancer (1 patient each) (Table 1). The 23 patients who completed the study received between 1 and 7 treatment cycles (mean = 2).

Pharmacokinetics

After a phase 1 study of EZN-2968, the dose is highly correlated with AUC (r=0.4, p<0.8, p<0.01), with a pattern consistent with dose-proportional PK within the studied range (Figure 3).

Pharmacodynamics

Concentrations of the following HIF-1 regulated gene products were determined: VEGF, ARF1, inducible nitric oxide synthase, bFGF, and collagen (Tables 3 and 4). Blood samples were collected at times 0 (pre-dose) and 2 hours (peak) after administration of EZN-2968 and analysis performed at 12-hour intervals, up to 60 hours from the last dose, and at the end-of-life visit. No consistent changes in these gene products were observed.

Antitumor Activity

Thus far, the best overall response (per RECIST) was stable disease (SD) for 4 patients and PD for 7 patients (who achieved SD). Of the 23 patients who were enrolled and treated, 2 patients had SD >97 and 62; 1 patient had RCC (66 days), and 1 patient had ovarian cancer (50 days).

Conclusions

EZN-2968, a novel HIF-1a-mRNA antagonist, was well tolerated in previously treated patients with advanced malignancies. No EZN-2968 was observed to be associated with serious adverse events. While the overall response rate of EZN-2968 in patients with advanced malignancies was low overall, EZN-2968 exhibited a two-component distribution (duration of stable disease was observed in two patients with advanced melanoma and two with advanced endometrial cancer, in one patient with renal cancer, and one patient with ovarian cancer. Dose escalation studies are underway.

References


*Poster 2564*