SN38 (10-hydroxy-7-ethyl-camptothecin) is a potent topoisomerase I inhibitor and the active moiety of CPT-11 (Camptosar, ) and irinotecan. Despite promising antitumoral potential in the laboratory, thus far SN38 itself has not been used as an anticancer tool in human due to its poor solubility in any pharmaceutically acceptable solvent. However, the poor solubility of SN38 can be vastly improved by conjugating to a water-soluble polymer. Hence, EZN-2208 (PEG-SN38) is a water-soluble polyethylene glycol (PEG) conjugate of SN38 with approximately 3.5 to 4.0 SN38 molecules attached to the optimally loaded 4-arm PEG backbone via a glycine linker (Figure1). EZN-2208 is in active broad spectrum of preclinical in vitro and in vivo models of multiple solid tumors and hematologic cancers, including in vivo model of CPT-11 resistance. In these models EZN-2208 had a significantly enhanced therapeutic effect compared with CPT-11.1,2,3 EZN-2208 enables increased solubility, parenteral delivery of SN38, longer circulating half-life, higher exposure of the active drug (SN38) in tumors, and greater preservation of the closed lactone ring (active form, Figure 2) in SN38 compared with SN38 derived from CPT-11.2,3,4 In animal models, EZN-2208 accumulates in tumors, where it releases SN38. The antitumor activity is attributed to higher exposure of tumors to SN38 via the peripheral accumulation of EZN-2208 in the tumor (enhanced permeability and retention (EPR) effect) compared with CPT-11.2,3 EZN-2208 also down-modulates mRNA of hypoxia-inducible factor-1a (HIF-1α).5

**Study Design**
- 3 + 3 design
- Dose expansion to 6 patients to determine the maximum tolerated dose (MTD)
- MTD dose expansion up to 10 patients
- 2 centers

**Objectives**
- Determine the MTD
- Determine the recommended Phase 2 dose
- Evaluate the safety and tolerability
- Determine the PK profile
- Detect preliminary evidence of antitumor activity

**Key Eligibility Criteria**
- Advanced or metastatic solid tumor or lymphoma; refractory to standard therapy
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
- Serum creatinine ≤ 1.5× upper limit of normal (ULN)
- Total bilirubin within normal limits
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2× ULN (≤ 1× if the increase is due to metastatic liver disease)

**Methods**
- Plasma concentrations of EZN-2208, SN38, and glucuronidated SN38 (SN38G) determined by HPLC with fluorescence detection

Note: The dose of EZN-2208 is stated as the dose of SN38 and not the dose of the conjugated compound.

**Pharmacokinetics**

All 41 patients provided data for PK analysis. Mean SN38 and SN38G concentrations in plasma are plotted in Figure 3.

**Conclusions**

EZN-2208, a novel agent, was well tolerated in previously treated patients with advanced malignancies: The MTD was neupetamin (1 patient), rection to the dose of 2.4. Kurzrock R, Wheler J, Hong DS, et al. Phase 1, first-in-human, dose-escalation study of EZN-2208, a novel anticancer agent, in patients with advanced malignancies: a Phase 1 dose-escalation study of EZN-2208 administered every 3 weeks 1 mg/m2. EZN-2208 administration every 3 weeks 1 mg/m2. Prolonged periods of SD, sometimes associated with tumor shrinkage, were observed. For some patients, the duration of EZN-2208 was longer than the duration of their prior therapy. EZN-2208 is being evaluated in a Phase 2 study in patients with metastatic CRC.

Also, see Poster C216 for a dose-escalation study of EZN-2208 administered every 3 weeks.

**Figure 2. Study scheme**

**Table 1. Demographics and Baseline Characteristics**

**Table 2. Drug-Related Adverse Events Reported in ≥ 10% of Patients**

**Table 3. Best Overall Responses**

**Figure 3. Mean (SD) SN38 and SN38G concentrations (ng/mL) in plasma after a 5-hour infusion of EZN-2208**

**Figure 4. Kaplan-Meier plot of median progression-free survival (PFS) for patients with metastatic colorectal cancer (MCC) enrolled in the Phase 1 dose-escalation study of EZN-2208**

* Asterisk is a known epithelial marker of EZN-Pharmacokinetics, Inc., and were company’s stock options and/or rights.