Poster
C221

EZN-2208, a novel anticancer agent, in patients with advanced malignancies: a Phase 1 dose-escalation study

Amita Patnaik, Kyriakos P. Papadopoulos, Muralidhar Beeram, Debbie Kee, Anthony W. Tolcher, Larry J. Schaaf, Sanaa Tahiri, Tanios Bekaii-Saab, Aby Buchbinder*

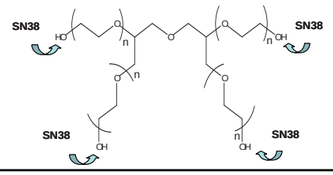
START (South Texas Accelerated Research Therapeutics), San Antonio, TX; Ohio State University, Columbus, OH; Enzon Pharmaceuticals, Inc., Bridgewater, NJ

Background

SN38 (10-hydroxy-7-ethyl-camptothecin) is a potent topoisomerase I inhibitor and the active moiety of CPT-11 (Camptosar®, irinotecan). Despite promising anticancer potential in the laboratory, thus far SN38 itself has not been used as an anticancer drug in humans due to its poor solubility in any pharmaceutically acceptable excipient. However, the poor solubility of SN38 can be vastly improved by PEGylation.

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 residue (Figure 1).[1]

Figure 1. EZN-2208 (PEG-SN38)[1]



EZN-2208 is active in a broad spectrum of preclinical in vitro and in vivo models of multiple solid tumors and hematologic cancers, including an in vivo model of CPT-11 resistance.[2,3] In these models, EZN-2208 had a significantly enhanced therapeutic effect compared with CPT-11.[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.[1,2]

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 preferential accumulation of EZN-2208 in the tumor (enhanced permeability and retention [EPR] effect) compared with CPT-11.[2] EZN-2208 also down-modulates mRNA of hypoxia-inducible factor-1α (HIF-1α).[3]

Clinical Study

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

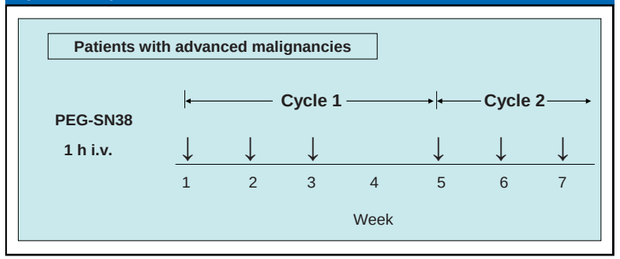
- Advanced and/or metastatic solid tumor or lymphoma; refractory to standard therapy
- Eastern Cooperative Oncology Group (ECOG) performance status = 0 to 2
- Serum creatinine ≤1.5 × upper limit of normal (ULN)
- Total bilirubin within normal limits
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × ULN (≤5 × ULN if the increase is due to metastatic liver disease)

Methods

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

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

Figure 2. Study schema



- Cycles repeat every 4 weeks (Figure 2).
- All patients screened for uridine diphosphate glucuronosyl-transferase isoform 1A1 (UGT1A1) genotype
- Dose level assigned based on UGT1A1 genotype
- Dose escalation based on drug-related toxicities observed during Cycle 1
- PK samples obtained after the first and third doses in Cycle 1
- Objective tumor response assessed every 6 to 8 weeks using the Response Evaluation Criteria in Solid Tumors (RECIST)

Interim Results

Patient and Treatment Information

At the time of the data cutoff, 43 patients had been enrolled. One patient in the 7 mg/m^2 cohort withdrew consent before receiving EZN-2208, and 1 patient in the 9 mg/m^2 cohort died before receiving EZN-2208. Of the 41 patients who received EZN-2208, the primary reasons for treatment termination were progressive disease (PD) (28 patients), withdrawn consent (4 patients), investigator's decision (2 patients), adverse events (AEs) (1 patient), death due to PD (1 patient), family decision (1 patient), and noncompliance (1 patient); 3 patients were still receiving study drug.

The AEs that resulted in the primary reason for treatment termination were lung infiltration, pulmonary embolus, respiratory failure, coagulopathy, cardiogenic shock, disease progression, and hepatic necrosis; all of these AEs resulted in death and were considered unlikely related to study drug.

The median age of the treated patients was 60 y (range: 35-85 y) (Table 1). Of the 41 treated patients, 21 (51%) were women and 20 (49%) were men; 93% of patients were white. Most patients had an ECOG performance status of 0 (37%) or 1 (54%). The UGT1A1 genotype was *1/*28 for 23 patients (56%), *1/*1 for 16 patients (39%), and *28/*28 for 2 patients (5%).

All 41 patients had received prior chemotherapy. Twenty patients (49%) had received prior irinotecan, and 1 patient (2%) had received prior topotecan. The median number of prior cytotoxic chemotherapies was 2 (range = 1 to 11). The most common tumor type was colorectal cancer (CRC) (59%) (Table 1).

The 41 patients who completed the study received between 1 and 15 treatment cycles (mean = 2).

Table 1. Demographics and Baseline Characteristics

Cohort	1	2	2H[a]	3	4	5	6	7	All
Dose (mg/m^2)	1	2	5	3.3	5	7	9	12	Patients
Number of patients treated	3	3	2	3	6	8	10	6	41
Median age in years (range)	67 (63-67)	69 (62-85)	58 (43-72)	53 (39-60)	54 (46-56)	60 (40-71)	61 (53-85)	57 (35-78)	60 (35-85)
Sex, n									
Female	2	2	2	0	3	5	5	2	21 (51%)
Male	1	1	0	3	3	3	5	4	20 (49%)
Cancer type, n									
Colorectal	0	2	0	3	2	6	6	5	24 (59%)
Breast	0	0	0	0	1	0	1	1	3 (7%)
Pancreatic	0	0	0	0	2	1	0	0	3 (7%)
Esophageal	0	1	0	0	0	0	1	0	2 (5%)
NSCLC	0	0	1	0	0	1	0	0	2 (5%)
Anal	0	0	1	0	0	0	0	0	1 (2%)
Carcinoid	0	0	0	0	1	0	0	0	1 (2%)
Gallbladder	0	0	0	0	0	0	1	0	1 (2%)
Gastric	1	0	0	0	0	0	0	0	1 (2%)
Ovarian	1	0	0	0	0	0	0	0	1 (2%)
Prostate	0	0	0	0	0	0	1	0	1 (2%)
Soft-tissue sarcoma	1	0	0	0	0	0	0	0	1 (2%)
Performance status (ECOG), n									
0	1	1	1	0	1	6	4	3	17 (41%)
1	2	2	1	3	3	2	6	3	22 (54%)
2	0	0	0	0	2	0	0	0	2 (5%)
UGT1A1 genotype, n									
*1/*28	2	2	0	1	4	6	6	2	23 (56%)
*1/*1	1	1	0	2	2	2	4	4	16 (39%)
*28/*28	0	0	2	0	0	0	0	0	2 (5%)

[a] Patients with homozygous *28/*28 UGT1A1 genotype.

Safety and Tolerability

Dose-limiting toxicities (DLTs) were Grade 3 febrile neutropenia (1 patient, 9 mg/m^2) and the inability to deliver the third week of therapy due to Grade 4 neutropenia (1 patient, 12 mg/m^2). Otherwise, neutropenia, when present, has been transient.

Dose escalation was stopped at the 12 mg/m^2 dose because at that dose, patients were not being fully dosed during Cycle 1 due to the onset of Grade 3 neutropenia on the day of drug administration (10 mg/m^2 is the recommended dose of EZN-2208 given every 3 weeks[4]).

All 41 treated patients had at least one treatment-emergent AE. The most commonly reported AEs (>25% of patients), regardless of relationship to study drug, were nausea (59%), diarrhea (54%), fatigue (49%), constipation and vomiting (39% each), alopecia (37%), anemia (29%), and anorexia (27%). Most AEs were Grade 1 or 2 in intensity.

The most frequently reported AEs (>20% of patients) considered likely related to study drug were nausea (49%), diarrhea (46%), fatigue (41%), alopecia (29%), neutropenia (24%), and vomiting (22%) (Table 2).

Grade 3 or 4 AEs considered likely related to study drug included neutropenia (17%), leukopenia (10%), and fatigue and peripheral neuropathy (5% each). The other drug-related Grade 3 or 4 AEs were reported in 1 patient each.

The Grade 5 AEs that resulted in the primary reason for treatment termination are summarized in the Patient and Treatment Information section. These AEs were considered unlikely related to study drug.

Table 2. Drug-Related Adverse Events Reported for >10% of Patients

AE / Cohort	1	2	2H[a]	3	4	5	6	7	All
Dose (mg/m^2)	1	2	5	3.3	5	7	9	12	Patients
Number of patients treated	3	3	2	3	6	8	10	6	41
Patients with ≥1 drug-related AE[b]	3	3	2	3	5	8	9	5	38 (93%)
Nausea	1	2	1	2	1	3	7	3	20 (49%)
Diarrhea	3	0	1	1	0	6	5	3	19 (46%)
Fatigue	1	1	1	1	1	3	6	3	17 (41%)
Alopecia	0	0	0	0	1	3	6	2	12 (29%)
Neutropenia	0	0	0	0	1	1	4	4	10 (24%)
Vomiting	0	0	1	0	2	2	2	2	9 (22%)
Anorexia	0	1	1	1	0	1	2	1	7 (17%)
Anemia	0	0	0	0	1	2	2	1	6 (15%)
Leukopenia	0	0	0	0	0	1	2	3	6 (15%)
Constipation	0	1	0	1	0	3	0	1	6 (15%)

[a] Patients with homozygous *28/*28 UGT1A1 genotype.
[b] Treatment-emergent AEs considered likely related to study drug.

Antitumor Activity

The best overall response was stable disease (SD) and PD for 18 patients each (44% each) (Table 3). The response was not evaluable for the other 5 patients (12%).

Table 3. Best Overall Response

Cohort	1	2	2H[a]	3	4	5	6	7	All
Dose (mg/m^2)	1	2	5	3.3	5	7	9	12	Patients
Number of patients treated	3	3	2	3	6	8	10	6	41
Stable disease, n	0	3	0	1	2	4	5	3	18 (44%)
Progressive disease, n	2	0	1	2	3	4	5	1	18 (44%)
Not evaluable, n	1	0	1	0	1	0	0	2	5 (12%)

[a] Patients with homozygous *28/*28 UGT1A1 genotype.

Of the 18 patients who achieved SD, 12 patients had CRC, 2 patients had breast cancer, 2 patients had esophageal cancer, 1 patient had NSCLC, and 1 patient had pancreatic cancer.

Prolonged SD (>90 days), sometimes associated with tumor shrinkage, was observed as a best response for 11 patients.

The tumor types and durations of SD for the 11 patients with prolonged SD are summarized below:

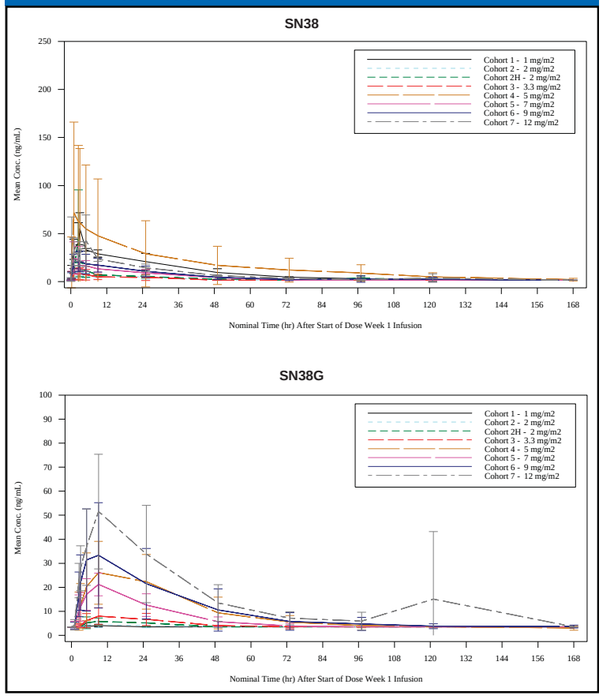
- 7 had CRC: 478 (↓), 186+, 174+, 108, 107, 107, and 92+ days
- 1 had heavily pretreated breast cancer: 106 days
- 1 had esophageal cancer: 162 days
- 1 had non-small-cell lung cancer (NSCLC): 120+ days
- 1 had pancreatic cancer: 239+ days

Four of the 7 patients with CRC who achieved prolonged SD had progressed after receiving prior irinotecan.

Pharmacokinetics

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

Figure 3. Mean (±SE) SN38 and SN38G concentrations (ng/mL) in plasma after a 1-hour infusion of EZN-2208



Conclusions

EZN-2208, a novel agent, was well tolerated in previously treated patients with advanced malignancies. The DLT was neutropenia ± fever, in distinction to the DLT of irinotecan. The MTD and recommended Phase 2 dose for EZN-2208 administered every 3 weeks is 9 mg/m^2. 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.[4]

References

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*Author is a full-time employee of Enzon Pharmaceuticals, Inc., and owns company's stock options and/or units.

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