Poster 427

Pharmacokinetics (PK) of EZN-2208, a novel anticancer agent, in patients (pts) with advanced malignancies: a phase I dose-escalation study

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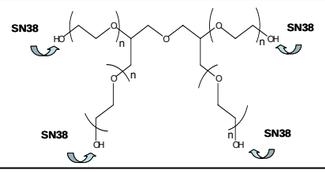
Background

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.

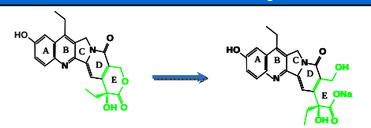
EZN-2208 (PEG-SN38) is a water-soluble polyethylene glycol (PEG) conjugate of SN38 with approximately 3.5 to 4.0 SN38 molecules attached to the optimally loaded 4-arm PEG backbone via a glycine residue (Figure 1).[1]

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



EZN-2208 enables increased solubility, parenteral delivery of SN38, longer circulating half-life, higher exposure of the active drug (SN38), and greater preservation of the closed lactone ring (active form, Figure 2) in SN38 compared with SN38 derived from CPT-11.[1,2]

Figure 2. Active form of SN38 has a closed lactone E-ring.[3]



In preclinical in vitro and in vivo models using multiple solid tumors, lymphomas, large tumors, resistant tumors (including an in vivo model of CPT-11 resistance), and sensitive tumors, EZN-2208 had a significantly enhanced therapeutic effect compared with CPT-11.[2] 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]

Clinical Study

Study Design

- 3 + 3 design
- Dose expansion to 6 pts to determine the maximum tolerated dose (MTD)
- MTD dose expansion up to 10 pts
- 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 anti-tumor activity

Key Eligibility Criteria

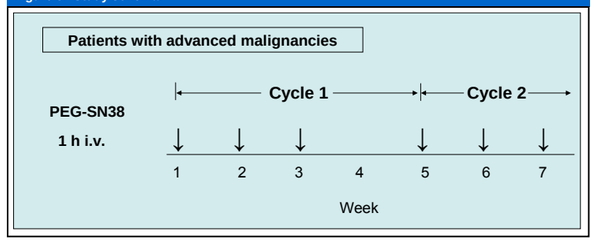
- Advanced and/or metastatic solid tumor or lymphoma; refractory to standard therapy
- Eastern Cooperative Oncology Group (ECOG) performance status = 0 to 2
- Serum creatinine ≤1.5 × upper limit of normal (ULN)
- Total bilirubin within normal limits
- Aspartate aminotransferase (AST) and alanine aminotransferase (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
- PK parameters estimated using noncompartmental model & analyzed using WinNonlin PK software (Version 5.1)

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

Figure 3. Study schema.



- Cycles: repeat every 4 weeks
- All pts screened for uridine diphosphate glucuronosyl-transferase isoform 1A1 (UGT1A1) genotype (*36, *1, *28, *37)
- Dose level assigned based on UGT1A1 genotype (Table 1)
- 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)

Results

Patient and Treatment Information

At the time of the data cutoff, 18 pts had been enrolled and treated. Three pts were still receiving study drug. For the other 15 pts, the reasons for discontinuation of EZN-2208 were progressive disease (PD) (12 pts), death (2 pts, discussed in Safety and Tolerability section), and withdrawn consent (1 pt).

The median age of the treated pts was 58 y (range: 39-85 y) (Table 1). Of the 18 treated pts, 10 (56%) were female and 8 (44%) were male; 12 pts (76%) had an ECOG performance status of 1 (Table 1). All pts were white. The UGT1A1 genotype was *1/*28 for 10 pts, *1 for 6 pts, and *28/*28 for 2 pts (Table 1).

All 18 pts had received prior chemotherapy (data not shown). Six pts had received prior irinotecan, and 1 pt had received prior topotecan. The median number of prior cytotoxic chemotherapies was 2 (range = 1 to 7).

Tumor types included colorectal cancer (CRC) (8 pts); pancreatic cancer (2 pts); hepatocellular carcinoma (1 pt); and abdominal, anal, breast, esophageal, gastric, lung, and ovarian cancers (1 pt each) (Table 1).

The 15 pts who completed the study received between 1 and 5 treatment cycles (mean = 2).

Table 1. Demographics and Baseline Characteristics

	Dose Cohort						All Patients
	Cohort 1 1 mg/m²	Cohort 2 2 mg/m²	Cohort 2H[a] 2 mg/m²	Cohort 3 3.3 mg/m²	Cohort 4 5 mg/m²	Cohort 5 7 mg/m²	
Pts enrolled and treated	3	3	2	3	6	1	18
Median age in years (range)	67 (63-67)	69 (62-85)	58 (43-72)	53 (39-60)	54 (46-56)	61 (61-61)	58 (39-85)
Sex, n							
Female	2	2	2	—	3	1	10
Male	1	1	—	3	3	—	8
Diagnosis, n							
Colorectal cancer	—	2	—	3	2	1	8
Pancreatic cancer	—	—	—	—	2	—	2
Abdominal cancer	1	—	—	—	—	—	1
Anal cancer	—	—	1	—	—	—	1
Breast cancer	—	—	—	—	1	—	1
Esophageal cancer	—	1	—	—	—	—	1
Gastric cancer	1	—	—	—	—	—	1
Hepatocellular carcinoma	—	—	—	—	1	—	1
Lung cancer	—	—	1	—	—	—	1
Ovarian cancer	1	—	—	—	—	—	1
Performance status (ECOG), n							
0	1	1	2	—	1	1	6
1	2	2	—	3	5	—	12
UGT1A1 genotype, n							
*1	1	1	—	2	2	—	6
*1/*28	2	2	—	1	4	1	10
*28/*28	—	—	2	—	—	—	2

[a] Pts with homozygous (*28/*28) UGT1A1 genotype.

Safety and Tolerability

No dose-limiting toxicities (DLTs) have been observed to date. No Grade 3 or 4 AEs were reported in Cycle 1 and hence were not considered DLTs.

All 18 pts had at least one treatment-emergent adverse event (AE). The most commonly reported AEs (>20% of pts) were nausea (50% of pts), vomiting (39% of pts), fatigue (33% of pts), anorexia and diarrhea (28% of pts each), and constipation (22% of pts) (data not shown). None of these AEs were considered dose limiting. Most AEs were Grade 1 or 2 in intensity.

The most frequently reported drug-related AEs were nausea (50% of pts), fatigue (33% of pts), and diarrhea (28% of pts) (Table 2). Four pts had Grade 3 AEs considered likely to be drug related: dehydration (1 pt), exertional dyspnea and prolonged coagulation time (1 pt), hypophosphatemia (1 pt), and thrombocytopenia (1 pt). One pt had Grade 4 AEs considered likely to be drug related: lung infiltration and respiratory failure. One pt in Cohort 3 and 2 pts in Cohort 4 died due to PD.

Table 2. Treatment-Emergent, Drug-Related Adverse Events Reported for >2 Pts

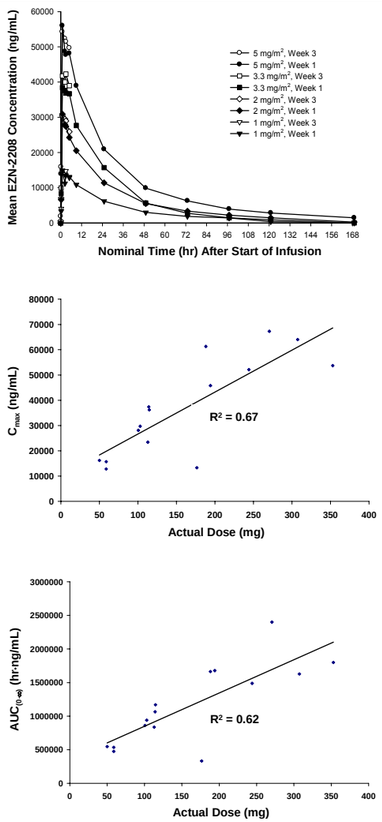
	Dose Cohort					All Patients n (%)
	Cohort 1 1 mg/m²	Cohort 2 2 mg/m²	Cohort 2H[a] 2 mg/m²	Cohort 3 3.3 mg/m²	Cohort 4 5 mg/m²	
Treated pts	3	3	2	3	6	18
Pts with ≥1 drug-related AE	3	3	2	3	5	16 (89)
Pts with:						
Nausea	3	2	1	1	2	9 (50)
Grade 1	1	2	—	—	1	4 (22)
Grade 2	2	—	1	1	1	5 (28)
Fatigue	3	—	1	1	1	6 (33)
Grade 1	2	—	—	—	—	2 (11)
Grade 2	1	—	1	1	1	4 (22)
Diarrhea	3	—	1	1	—	5 (28)
Grade 1	2	—	1	1	—	4 (22)
Grade 2	1	—	—	—	—	1 (6)
Vomiting	1	—	1	—	2	4 (22)
Grade 1	1	—	—	—	1	2 (11)
Grade 2	—	—	1	—	1	2 (11)
Anorexia	1	1	1	—	—	3 (17)
Grade 1	1	1	—	—	—	2 (11)
Grade 2	—	—	1	—	—	1 (6)
Constipation	1	2	—	—	—	3 (17)
Grade 1	1	2	—	—	—	3 (17)

[a] Pts with homozygous (*28/*28) UGT1A1 genotype.

Pharmacokinetics

Fifteen of the 18 pts enrolled in the first 4 cohorts provided data for PK analysis (Figure 4, Table 3).

Figure 4. Mean EZN-2208 plasma concentration, C_{max}, and $AUC_{(0-\infty)}$ after a 1-hour infusion of EZN-2208 at 1 of 4 dose levels.



Pharmacokinetics (continued)

There is very little intra-patient variability based on maximum plasma concentration (C_{max}) comparisons between the first and the third doses, indicating no plasma accumulation.

The dose is highly correlated with C_{max} and area under the drug concentration-time curve (AUC) (R^2 = 0.67 and 0.62, respectively) and, consistent with the concentration-time curve patterns, indicates that EZN-2208 PK most likely is dose proportional (Figure 4).

The volume of distribution (Vd) of EZN-2208 is small (mean = 6.6 l) (data not shown), the C_{max} is high, and the half-life is long (mean = 31.1 hours) (Table 3), consistent with PK results for other PEG derivatives.

Plasma concentrations of SN38 (Table 3) and SN38G are negligible compared to the parent compound, EZN-2208 (PEG-SN38).

The PK profile of EZN-2208 is very different from that of irinotecan, which has a very large Vd (136-250 l) and a comparatively low C_{max} (~1,000 times lower than that of EZN-2208).[3]

SN38, the active metabolite of EZN-2208 and irinotecan, follows a similar distribution pattern compared to its parent compounds in both cases.[3]

Table 3. PK Parameters After First 1-Hour Infusion of EZN-2208

Dose[a] (mg/m²)	EZN-2208[b]			SN38[b]		
	C_{max}[a] (µg/mL)	$AUC_{(0-\infty)}$[a,c] (hr·µg/mL)	Terminal $t_{½}$ (hr)	C_{max} (ng/mL)	$AUC_{(0-t)}$[c] (hr·ng/mL)	Terminal $t_{½}$ (hr)
1	14.9 ± 1.8	520 ± 38	31.1 ± 2.5	57.3 ± 13.3	1388 ± 293	26.5 ± 4.6
2	29.8 ± 6.4	988 ± 166	32.9 ± 6.7	24.8 ± 31.6	305 ± 121	26.5 ± 4.6
3.3	40.1 ± 24.5	1225 ± 773	21.3 ± 4.9	11.5 ± 7.0	227 ± 179	27.3 ± 3.3
5	59.3 ± 7.5	1829 ± 402	39.1 ± 2.3	103.4 ± 104.2	3196 ± 3138	29.9 ± 3.8

[a] SN38 equivalents.
[b] Mean ± standard deviation.
[c] $AUC_{(0-t)}$, t is time of last measurable concentration.

Antitumor Activity

The best overall response was stable disease (SD) for 6 pts and PD for 6 pts (Table 4). Three pts had not completed Cycle 1 at the data cutoff and thus were not evaluable; response information was not available for the other 3 pts.

Of the 6 pts who achieved SD, 4 pts had CRC (duration of SD = 54, 54+, 117, and 294+ days); 1 pt had breast cancer (129 days); and 1 pt had esophageal cancer (92+ days). Three pts had SD lasting at least 4 months.

Three of the 4 pts with CRC who achieved SD had progressed after receiving prior irinotecan.

Table 4. Best Overall Response

	Dose Cohort						All Patients n (%)
	Cohort 1 1 mg/m²	Cohort 2 2 mg/m²	Cohort 2H[a] 2 mg/m²	Cohort 3 3.3 mg/m²	Cohort 4 5 mg/m²	Cohort 5 7 mg/m²	
Treated pts	3	3	2	3	6	1	18
Stable disease	—	3	—	1	2	—	6 (33)
Progressive disease	2	—	2	1	1	—	6 (33)
Not evaluable	1	—	—	1	1	—	3 (17)
Pending data	—	—	—	—	2[b]	1[c]	3 (17)

[a] Pts with homozygous (*28/*28) UGT1A1 genotype.
[b] One pt ongoing, and one pt died during Cycle 1.
[c] Pt ongoing.

Conclusions

EZN-2208, a novel agent, was well tolerated in pretreated pts with advanced malignancies. No DLTs have been observed to date, and enrollment is ongoing. A qualitative assessment of the EZN-2208 PK data indicated that the AUC appears to increase in a dose-proportional manner. PK data demonstrated high AUC and prolonged exposure to SN38. The $t_{1/2}$ of EZN-2208 was about 31 hours.

References

1. Zhao H, Rubio B, Sapra P, et al. Novel prodrugs of SN38 using multi-arm polyethylene glycol (PEG) linkers. *Bioconjug Chem*. 2008;19:849-859.
2. Sapra P, Zhao H, Mehlig M, et al. Novel delivery of SN38 markedly inhibits tumor growth in xenografts, including a camptothecin-11–refractory model. *Clin Cancer Res*. 2008;14:1888-1896.
3. Chabot GG. Clinical pharmacokinetics of irinotecan. *Clin Pharmacokin*. 1997;33:245-259.

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

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