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

A. Patrawala1, M. Goldstein2, C. Takimoto3, B. Adunbanke1, B. Patel3, P. R. Manley3, E. Gillies1, C. Longley3, A. Bushbinder4

1START (South Texas Accelerated Research Therapeutics), San Antonio, TX, USA; 2Ohio State University, Columbus, OH, USA; Enzon Pharmaceuticals, Inc., 3Bridgewater and 4Piscataway, NJ, USA

Background

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 PEG backbone via a glycosyl residue (Figure 1).2

Clinical Study

Study Design

- 2 × 2 design
- Dose expansion to 6 pts to determine the maximum tolerated dose (MTD)
- MTD dose expansion up to 16 pts

Objectives

- Determine the MTD
- Determine the recommended Phase II dose
- Evaluate the safety and tolerability
- Determine the PK profile

Key Eligibility Criteria

- Advanced and/or metastatic solid tumor or lymphoma; refractory to standard therapy
- Eastern Cooperative 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) ≤ 5 × ULN (5 ULN if 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 & analysed 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.

Results

Patient and Treatment Information

At the time of the data cutoff, 10 pts had been enrolled and treated. Three pts were still receiving study drug. For the other 10 pts, the reasons for discontinuation of EZN-2208 were progressive disease (PD) (2 pts), withdrawal of consent (1 pt), treatment intolerance (1 pt), patient death (3 pts), and other causes (1 pt). The median age of the treated pts was 58 y (range: 43-85 y) (Table 1). Of the 16 treated pts, 16 (100%) were female and 8 (50%) were male. 14 pts (93%) had an ECOG performance status of 0 (Table 1). All pts with UGT1A1 genotype were *28/*28 (12/12). After a 1-hour infusion of EZN-2208, six pts had received prior chemotherapy (data not shown). Six pts had received prior vinorelbine, and 3 pts had received prior trastuzumab. The median number of prior cytotoxic chemotherapies was 2 (range: 1-3) (Table 1).

Tumor types included colorectal cancer (CRC) (10 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 10 pts who completed the study remained on 3 to 5 treatment cycles (mean = 2).

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.

No Grade 3 or 4 AEs were reported in Cycle 1 and hence were not considered DLTs.

Pharmacokinetics

Six of the 10 pts enrolled in the first 4 cohorts provided data for PK analysis (Figure 4, Table 2).

The most frequently reported drug-related AEs were nausea (50% of pts), fatigue (50% of pts), and diarrhea (28% of pts) (Table 2). Four pts had Grade 3 AEs considered likely to be drug related: asthenia (1 pt), neutropenia (1 pt), and thrombocytopenia (1 pt). On day 8, 3/16 pts had Grade 3 drug-related lung infiltration and respiratory failure. One pt in Cohort 3 and 2 pts in Cohort 1 died related to PD.

Pharmacokinetics (continued)

There is very little intrapatient variability based on maximum plasma concentration (Cmax) between the first and the third doses, indicating no plasma accumulation.

The dose is highly correlated with Cmax and area under the concentration-time curve (AUC) (R2 = 0.67 and 0.62, respectively) and, consistent with the concentration-time curve patterns, indicates that EZN-2208 PK most likely in dose proportional (Figure 4).

The volume of distribution (Vd) of EZN-2208 is small (mean = 4.6 ± 1.1 L) (data not shown), the Cmax is high, and the t1/2 is long (mean = 21.1 ± 7.0 h) (Table 2), consistent with results from 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 Cmax (2-3). This could be because of the reduced plasma accumulation of EZN-2208 in the tumor (enhanced permeability and retention [EPR] effect).

Table 1. Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Dose 1 (mg/m2)</th>
<th>Dose 2 (mg/m2)</th>
<th>Dose 3 (mg/m2)</th>
<th>Dose 4 (mg/m2)</th>
<th>Dose 5 (mg/m2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>58 (39-85)</td>
<td>58 (43-72)</td>
<td>58 (39-85)</td>
<td>58 (43-72)</td>
<td>58 (43-72)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2 (2/2)</td>
<td>2 (2/2)</td>
<td>2 (2/2)</td>
<td>2 (2/2)</td>
<td>2 (2/2)</td>
</tr>
<tr>
<td>Female</td>
<td>8 (8/8)</td>
<td>8 (8/8)</td>
<td>8 (8/8)</td>
<td>8 (8/8)</td>
<td>8 (8/8)</td>
</tr>
<tr>
<td>Prior treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>w/o vinorelbine</td>
<td>10 (10/10)</td>
<td>10 (10/10)</td>
<td>10 (10/10)</td>
<td>10 (10/10)</td>
<td>10 (10/10)</td>
</tr>
<tr>
<td>Maintenance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>w/o irinotecan a</td>
<td>10 (10/10)</td>
<td>10 (10/10)</td>
<td>10 (10/10)</td>
<td>10 (10/10)</td>
<td>10 (10/10)</td>
</tr>
</tbody>
</table>

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

References


EORTC-NOA-HANC, Genève, Switzerland; 20 October 2008