Poster A216

Results of a Phase 1, open-label, dose-escalation study evaluating the safety and tolerability of EZN-3042, a survivin messenger ribonucleic acid (mRNA) antagonist, administered with or without docetaxel in adult patients with advanced solid tumors or lymphoma

Anthony W. Tolcher,[1] Amita Patnaik,[1] Kyriakos P. Papadopoulos,[1] James Agnew,[1] François M. Lokiec,[2] Keyvan Rezaï,[2] Stacey Kalambakas,[†] Aby Buchbinder[3*]

[1]START (South Texas Accelerated Research Therapeutics), San Antonio, TX, USA; [2]René Huguenin Hospital, Institut Curie, Saint-Cloud, France; [3]Enzon Pharmaceuticals, Inc., Piscataway, NJ, USA

Background

Survivin, the smallest member of the inhibitors of apoptosis (IAP) gene family, functions as an essential regulator of mitosis and apoptosis as well as a promoter of tumor-associated angiogenesis.[1,2]

Survivin is rarely expressed in most normal adult tissues,[1] but it is preferentially and highly expressed in many types of cancer.[3-5] Overexpression of survivin in many cancers is correlated with an increased rate of disease recurrence and reduced survival.[6,7] Increased survivin expression also is associated with increased risk of metastasis, depth of invasion, and locoregional occurrence.[7] Down-regulation of survivin may have broad therapeutic application.

The survivin mRNA antagonist, designated EZN-3042, is a potent locked nucleic acid (LNA) antisense oligonucleotide that specifically down-modulates survivin mRNA and protein.[8-10] The oligonucleotide EZN-3042 is composed of 16 monomeric units, a 16-mer, of which 7 DNA nucleotides are replaced with LNA nucleotides. The sequence of EZN-3042 is 5′CTCAatccatggCAGc-3′. Capital letters denote LNA monomers, and lowercase letters denote DNA monomers.

When transfected into tumor cells, the survivin antagonist was a highly potent inhibitor of survivin expression in vitro (IC_{50} <5 nM).[8,10] Preclinically, EZN-3042 enhanced apoptotic and antitumor effects of taxanes.[9,10] When EZN-3042 was tested in combination with subtherapeutic doses of paclitaxel in xenograft models of human lung cancer, EZN-3042 significantly enhanced apoptotic and antitumor effects of taxanes.[9,10] EZN-3042 potentiated the effect of chemotherapy and resulted in a decrease in tumor progression in mouse primary xenograft model of relapsed acute lymphoblastic leukemia, and in combination with chemotherapy sensitized drug-resistant cells to chemotherapeutic regimens preclinically.[11,12]

Single-Agent EZN-3042 Results

Single agent results were previously reported.[13]

EZN-3042 was generally well tolerated in 24 previously treated patients with advanced malignancies.

Dose-limiting toxicity (DLT), was observed in 3 patients who had received EZN-3042 at a dose of 8 mg/kg: reversible Grade 3 increased aspartate or alanine aminotransferase (AST or ALT).

The MTD for single-agent EZN-3042 was 6.5 mg/kg.

The most commonly reported AEs (>4 patients), regardless of relationship to study drug, were fatigue (11 patients); tumor pain and increased AST (10 patients each); increased ALT (9 patients); anorexia (7 patients); and diarrhea, nausea, and rash (5 patients each).

The best response for single-agent EZN-3042 was stable disease in 5 patients.

Both the drug concentration-time curve (AUC) and the maximum drug concentration (C_{max}) increased in an approximately dose-proportional manner. There appeared to be little or no accumulation of drug during the fourth week through Day 28. The median elimination half-life of EZN-3042 was approximately 1.85 hours (range = 1.30–5.00 hours), the mean volume of distribution of the central compartment was 12.95 L (range = 6.38–18.99 L), and the mean clearance was 5.1 L/h (1.6–6.9 L/h).

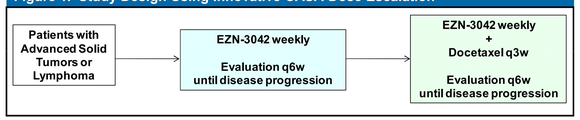
Clinical Study

Study Design

- Combination after single agent (CASA) modified Fibonacci dose-escalation (Figure 1)
  - Allows one to follow safety and efficacy for the same patient as he/she progresses from single-agent to combination treatment. After determination of the single agent MTD, patients could be treated directly with the combination treatment.
  - Independent dose escalation (3 + 3) for single agent and for combination; dose escalation based on toxicities observed during Cycle 1 of single agent or combination, respectively.

Clinical Study (continued)

Figure 1. Study Design Using Innovative CASA Dose Escalation



- EZN-3042 2-hour intravenous (i.v.) infusion weekly
- Docetaxel (Taxotere®) 75 mg/m² i.v. infusion every 3 weeks
- Objective tumor response assessed every 6 weeks using the Response Evaluation Criteria in Solid Tumors (RECIST)
- Continue until progressive disease (PD) or unacceptable toxicity

Objectives

Primary Objectives

- Determine the maximum tolerated dose (MTD)
- Determine the recommended Phase 2 dose
  - EZN-3042 administered as a single agent
  - EZN-3042 administered in combination with docetaxel

Secondary Objectives

- Evaluate safety and tolerability of each regimen
- Determine the pharmacokinetic (PK) profile
- Evaluate the pharmacodynamic profile of EZN-3042
- Detect preliminary evidence of antitumor activity

Methods

- Plasma concentrations of EZN-3042 and docetaxel determined by immunoassay using hybridization of capture and detection oligonucleotides; lower limit of quantitation = 0.25 ng/mL
- PK parameters estimated using a Bayesian approach (Monolix Version 31s; http://wfn.software.monolix.org)

Results

Patient and Treatment Information

EZN-3042 + Docetaxel

Sixteen patients received the combination regimen (Table 1). The median age was 66 y (range: 44-75 y) (Table 1). Of the 16 patients, 9 (56%) were men and 7 (44%) were women; 15 patients (94%) were white. Fourteen patients (88%) had an ECOG performance status of 0 or 1.

Tumor types included prostate cancer (6 patients); breast cancer (3 patients), pancreatic cancer (2 patients); and NSCLC, leiomyosarcoma, gastric, squamous cell carcinoma of the tongue, and squamous cell carcinoma of unknown primary origin (1 patient each). The 16 patients who completed the study received between 1 and 9 cycles (median = 2).

Ten patients received EZN-3042 + docetaxel after progressing on single agent EZN-3042. Six patients were treated directly with the combination regimen.

Table 1. EZN-3042 + Docetaxel: Demographics and ECOG Performance Status

	Cohort 1C 2.5 mg/kg EZN-3042 + Docetaxel	Cohort 2C 5 mg/kg EZN-3042 + Docetaxel	Cohort 2C-1 6.5 mg/kg EZN-3042 + Docetaxel	All Patients n (%)
Patients treated	7	3	6	16
Age, years				
Median	69	54	67	66
Range	57-75	44-55	56-73	44-75
Sex, n				
Male	6	0	3	9
Female	1	3	3	7
ECOG performance status, n				
0	3	0	3	6
1	4	1	3	8
2	0	2	0	2

Results (continued)

Safety and Tolerability

EZN-3042+ Docetaxel

Adverse events

Fifteen of the 16 patients (94%) had at least one treatment-emergent AE. Most AEs were Grade 1 or 2. The most commonly reported AEs (>2 patients), regardless of relationship to study treatment, were fatigue (10 patients); neutropenia (8 patients); peripheral sensory neuropathy, alopecia (6 patients each); nausea, vomiting, constipation, anorexia, and tumor pain (5 patients each); and leukopenia, diarrhea, mucosal inflammation, cough, and dyspnea (3 patients each).

Thirteen patients (81%) who received combination treatment had Grade 3/4 AEs regardless of relationship to study treatment, the most common (>1 patient) of which were neutropenia (8 patients), leukopenia (3 patients), and peripheral sensory neuropathy (2 patients). Two patients in the 6.5 mg/kg EZN-3042 + docetaxel cohort experienced Grade 4 AEs not related to study treatment. One patient had Grade 4 neutropenia and another patient had Grade 4 obstructive airway disorder. Both of these events resolved. One patient (5 mg/kg EZN-3042 + docetaxel) died due to PD within 30 days of last dose.

Treatment-related adverse events

Thirteen of 16 patients (81%) had at least one treatment-related AE, most of which were Grade 1 or 2. The most frequently reported treatment-related AEs (in > 2 patients) were fatigue (9 patients), alopecia (6 patients), neutropenia (5 patients), nausea, anorexia, and peripheral sensory neuropathy (4 patients each), and leukopenia (3 patients) (Table 2).

Eight patients (50%) had treatment-related Grade 3/4 AEs: neutropenia (5 patients), leukopenia (3 patients), increased ALT and increased AST (1 patient each), all of which resolved. Peripheral sensory neuropathy (2 patients) and Grade 4 Guillain-Barre syndrome (1 patient) remain unresolved.

Dose-limiting toxicity

Grade 3 neutropenic fever was observed in 1 patient who received EZN-3042 (2.5 mg/kg) + docetaxel; the event resolved within 7 days of onset. Another DLT of Grade 3 AST/ALT was observed in 1 patient who received EZN-3042 (6.5 mg/kg) + docetaxel; the events resolved within 30 days of onset. The maximum tolerated dose (MTD) was 6.5 mg/kg EZN-3042 + docetaxel. The dose of 6.5 mg/kg, which was determined to be the MTD for EZN-3042 as a single agent, was the highest dose evaluated in combination with docetaxel.

Table 2. EZN-3042 + Docetaxel: Treatment-Related Adverse Events Reported for > 1 Patient

	Cohort 1C 2.5 mg/kg EZN-3042 + Docetaxel	Cohort 2C 5 mg/kg EZN-3042 + Docetaxel	Cohort 2C-1 6.5 mg/kg EZN-3042 + Docetaxel	All Patients n (%)
Patients treated	7	3	6	16
Patients with ≥ 1 treatment-related AE	6	3	4	13 (81)
Fatigue	5	2	2	9 (56)
Alopecia	4	1	1	6 (38)
Neutropenia	5	0	0	5 (31)
Nausea	3	0	1	4 (25)
Anorexia	4	0	0	4 (25)
Peripheral sensory neuropathy	1	0	3	4 (25)
Leukopenia	3	0	0	3 (19)
Vomiting	2	0	0	2 (13)
Pruritis	1	0	1	2 (13)
Constipation	1	0	1	2 (13)
Mucosal inflammation	1	1	0	2 (13)
ALT increased	1	0	1	2 (13)

Pharmacokinetics

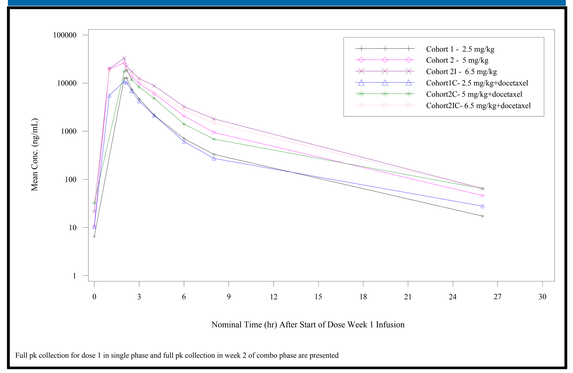
EZN-3042 + Docetaxel

Thirteen patients who received EZN-3042 + docetaxel provided data for PK analysis. EZN-3042 was infused over 2 hours and docetaxel was infused over 1 hour. The maximum drug concentration (C_{max}) appears to be increasing in an approximately dose-proportional manner and was similar in the single agent and combination cohorts. (Figure 2).

The mean elimination half-life of EZN-3042 in combination with docetaxel was approximately 1.99 hours and similar across the 3 cohorts (range = 1.82–2.07 hours). The mean volume of distribution of the central compartment was 12.91 L (range = 9.25–15.07 L) and the mean clearance was 4.60 L/h (3.53–5.27 L/h) .

Results (continued)

Figure 2. Mean Concentration of EZN-3042 in the Single Phase vs the Combination Phase



Full pk collection for dose 1 in single phase and full pk collection in week 2 of combo phase are presented

Antitumor Activity

EZN-3042+ Docetaxel

The best response for EZN-3042 + docetaxel was partial response in 1 patient with prostate cancer (2.5 mg/kg, 124+ days) (Table 3).

Table 3. Best Overall Response

	Cohort 1C 2.5 mg/kg EZN-3042 + Docetaxel	Cohort 2C 5 mg/kg EZN-3042 + Docetaxel	Cohort 2C-1 6.5 mg/kg EZN-3042 + Docetaxel	All Patients n (%)
Patients treated	7	3	6	16
Partial response	1	0	0	1
Stable disease	3	0	2	5
Progressive disease	1	2	3	6
Not evaluated	2	1	1	4

Conclusions

EZN-3042 + docetaxel was well tolerated in previously treated patients with advanced malignancies. The MTD for EZN-3042 + docetaxel was 6.5 mg/kg. C_{max} appeared to increase in a dose proportional manner. There was one partial response in a patient with prostate cancer after treatment with 2.5 mg/kg EZN-3042 + docetaxel. A window-of-opportunity study of EZN-3042 in combination with chemotherapy is ongoing in pediatric patients with relapsed acute lymphoblastic leukemia.[14]

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14. ClinicalTrials.gov NCT01186328

* Author is a full time employee of Enzon Pharmaceuticals, Inc. and own company stock options and/or units
† Author formerly employed by Enzon Pharmaceuticals, Inc.

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