Poster
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Phase 2, open-label study of EZN-2208 (PEG-SN38) in patients with previously treated metastatic breast cancer

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Abstract

Background:

EZN-2208 is a water-soluble PEGylated conjugate of SN38 that results in parenteral delivery, increased solubility, higher exposure, and longer apparent half-life of SN38, as well as more profound deoxyribonucleic acid (DNA) damage and inhibition of angiogenesis, than irinotecan. EZN-2208 results in prolonged exposure of tumors to SN38 via preferential accumulation of EZN-2208 in the tumor and prolonged release of SN38 in the blood.

Methods:

EZN-2208 9 mg/m^2 (SN38 equivalence) was delivered as a 60-minute IV infusion, weekly for 3 wks in 4-wk cycles. The primary objective was to determine the overall response rate (RR) in female patients with metastatic breast cancer who had received prior adjuvant or metastatic therapy with either 1) anthracycline and taxane (AT) or 2) anthracycline, taxane, and capecitabine [Xeloda®] (ATX). Secondary objectives included evaluation of RR based on tumor receptor status, duration of response, progression-free survival (PFS), overall survival (OS), and safety.

Results:

Female patients with metastatic breast cancer (n=164) were treated with a median (range) of 3 (0.3–19.3) cycles of EZN-2208. The objective response rate (RR) was 21% for AT and 11% for ATX. The clinical benefit rate (%CR + %PR + %SD ≥6 months) was 37% and 21% in the AT and ATX cohorts, respectively. For the AT and ATX cohorts, the median duration of response was 4.2 and 5.2 months, the median PFS was 3.8 and 3.4 months, and the median OS was 10.5 and 8.0 months, respectively. The most common reported drug-related adverse events were neutropenia, diarrhea, and leukopenia.

Conclusions:

EZN-2208 is active in patients with previously treated metastatic breast cancer (MBC). The activity is similar in patients with hormone- and nonhormone expressing breast cancer, indicating that EZN-2208 is a promising therapy for the triple-negative breast cancer population. The safety profile of EZN-2208 is acceptable with good tolerability in most patients.

Background

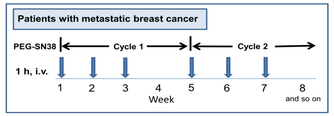
- Despite the numerous therapies available, there remains a need for new effective therapy for patients with previously-treated MBC
- EZN-2208 (polyethylene glycol [PEG]-SN38) is a water soluble PEGylated conjugate of SN38
- SN38 is the active metabolite of irinotecan (CPT-11, Camptosar) and has 100 to 1,000-fold more potent in-vitro cytotoxic activity than its prodrug, irinotecan[1]
- PEGylation of SN38 increases its solubility and half-life, yielding higher SN38 exposure[2,3]
- EZN-2208's properties of interest:
  - Compared with irinotecan – higher tumor exposure, longer half-life, more profound DNA damage and inhibition of angiogenesis[4,5]
  - Preferential accumulation in tumors secondary to enhanced permeability and retention (EPR) effect
  - Marked anti-cancer activity in *in-vivo* models of triple negative[5] and HER2+, trastuzumab-resistant breast cancer[6,7]
  - Efficacy in > 15 other pre-clinical models, involving many tumor types[4,6]

Objectives

- Phase 2, multicenter, open-label, noncomparative study of single agent EZN-2208 (ClinicalTrials.gov Identifier: NCT01036113) in female patients with previously treated metastatic breast cancer
- Primary objective: Determine overall response rate (RR) in two distinct cohorts
  - Patients previously treated with AT
  - Patients previously treated with ATX
- Secondary objectives: Evaluate duration of response, PFS, OS, RR based on tumor receptor status, and safety

Study Design

- Single agent EZN-2208 9 mg/m^2 was administered as a 60-minute intravenous (IV) infusion weekly for 3 weeks in 4-week cycles



Key eligibility criteria

- Prior therapy:
  - AT Cohort: Prior anthracycline and taxane (adjuvant or metastatic), ≤2 prior lines of cytotoxic therapy for MBC
  - ATX Cohort: Prior anthracycline, taxane, and capecitabine (adjuvant or metastatic); ≤4 prior lines of cytotoxic therapy for MBC
- Age ≥18 years
- Progression of disease on prior therapy or intolerance of therapy
- Patients with HER2+ tumors must have received prior trastuzumab
- Patients with ER+ tumors must have received prior hormone therapy
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2
- Laboratory parameters:
  - Absolute neutrophil count (ANC) ≥1,000/ L
  - Platelet count ≥75,000/ L
  - Total bilirubin within normal limits
  - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 ULN or ≤5 ULN if increase due to metastatic disease to liver

Response and safety

- Response was evaluated using RECIST (Version 1.1)[8]
- Safety evaluated using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v 4.0)

Demographics

- A total of 164 patients stratified into cohorts AT and ATX were enrolled from Dec. 11, 2009 until Aug. 10, 2011

	AT	ATX
Patients treated	81	83
Patients remaining on study	24 (30%)	8 (10%)
Median age	56 (30–84)	55 (36–83)
Median disease duration (yrs)	4.6	7.6
# Prior cytotoxic regimens for MBC		
≤ 2 regimens	81 (100%)	31 (37%)
> 2 regimens	0	52 (63%)
Anthracycline (A)	80 (99%)	80 (96%)
Taxane (T)	81 (100%)	82 (99%)
Capecitabine (X)	0	83 (100%)
ECOG		
0	32 (40%)	29 (35%)
1	45 (56%)	50 (60%)
2	4 (5%)	4 (5%)
Receptor status		
ER+	43(53%)	58 (70%)
HER2+	8 (10%)	10 (12%)
Triple Negative	35 (43%)	20 (24%)

Data as of October 31, 2011

Preliminary Results

Treatment Exposure

- The median number of months of treatment was similar for both cohorts
  - AT: 3.0 (0.3–19.0+)
  - ATX: 3.0 (0.3–19.3+)

Efficacy

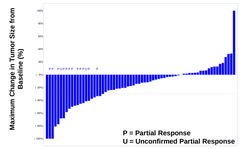
Primary and Secondary Endpoints

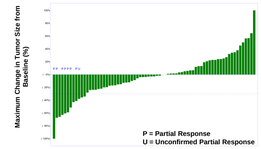
		AT	ATX
Patients (n)		81	83
Treated		11	8
Not Evaluable		70	75
Primary Endpoint		**n (%)**	
Overall	RR[1]	15[2] (21%)	8[3] (11%)
	Clinical Benefit	26 (37%)	16 (21%)
Secondary Endpoints			
Triple Negative	RR	7 (23%)	3 (19%)
	Clinical Benefit	9 (30%)	3 (19%)
ER+	RR	7 (19%)	5 (9%)
	Clinical Benefit	15 (41%)	13 (24%)
HER2+	RR	1 (17%)	0
	Clinical Benefit	2 (33%)	3 (30%)
		Months (95% CI)	
Median Duration of Response		4.2 (3.7–5.8)	5.2 (3.7–13.0)
Median PFS		3.8 (3.1–5.5)	3.4 (1.9–3.9)
Median OS		10.5 (8.9–11.9)	8.0 (6.9–12.9)
		Percent (95% CI)	
6-month PFS		35% (24%–47%)	24% (14%–33%)

[1]RR = (PR+uPR); [2]12 PR, 3 unconfirmed PR; [3]7 PR, 1 unconfirmed PR; Data as of October 31, 2011

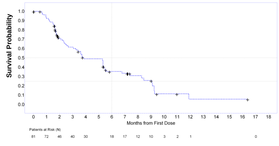
Figures AT ATX

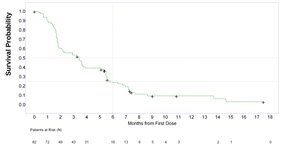
Maximum Change From Baseline



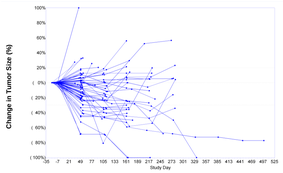


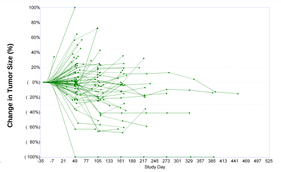
Progression Free Survival





Change in Tumor Size Over Time





Safety

Adverse Events

	AT		ATX	
Serious drug-related AEs seen in ≥ 5% of patients in at least 1 cohort				
Any	10 (12%)		8 (10%)	
Dehydration	5 (6%)		5 (6%)	
Diarrhea	3 (4%)		6 (7%)	
Nausea	-		4 (5%)	
Vomiting	-		4 (5%)	
Drug-related AEs seen in ≥5% of patients in at least 1 cohort				
	Grade 3	**Grade 4**	**Grade 3**	**Grade 4**
Any	53 (65%)		41 (49%)	
Neutropenia	19 (23%)	19 (23%)	16 (19%)	13 (16%)
Diarrhea	10 (12%)	-	9 (11%)	-
Leukopenia	9 (11%)	3 (4%)	7 (8%)	-
Dehydration	5 (6%)	-	6 (7%)	-
Nausea	2 (2%)	-	6 (7%)	-
Fatigue	4 (5%)	-	3 (4%)	-

Data as of October 31, 2011

Conclusions

- In this preliminary analysis, EZN-2208 demonstrated significant activity in patients with metastatic breast cancer previously treated with AT or ATX

AT	ATX
• 21% RR (PR+uPR)	• 11% RR (PR+uPR)
• 35% 6-month PFS	• 24% 6-month PFS

- Significant activity was observed in many patient subsets including patients with triple-negative breast cancer (AT: 23% RR, 30% clinical benefit; ATX: 19% RR, 19% clinical benefit)
- The safety profile of EZN-2208 was acceptable with good tolerability in most patients
- Further evaluation of EZN-2208 in this population is warranted

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*Noah Berkowitz and Aby Buchbinder are full-time employees of Enzon Pharmaceuticals, Inc., and own company stock options and/or units. There are no disclosures from any of the other authors.