Final analysis of Phase 2 study of EZN-2208 (PEG-SN38) in metastatic breast cancer (MBC) demonstrates activity in patients with triple negative breast cancer (TNBC) and in platinum pretreated patients

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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:

Patients with MBC (n=164) were treated with a median (range) of 3 (1–24) cycles of ENZ-2208. The objective response rate (RR) was 25% for AT and 11% for ATX. The clinical benefit rate (CBR=%CR + %PR + %SD ≥6 months) was 43% and 29% in patients in the AT and ATX cohorts, respectively. The RR and CBR among ER+ patients were 15% (14/92 pts) and 39% (36/92 pts). In patients who progressed during or within 30 days of prior platinum-containing regimens (Platinum Progressors), the CBR was 18% (7/40 pts). Among triple negative breast cancer (TNBC) patients, the RR and CBR were 23% (11/47 pts) and 32% (15/47 pts). For TNBC, Platinum Progressors, the CBR was 18% (4/22 pts). Overall, the most common reported study 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 non-hormone 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

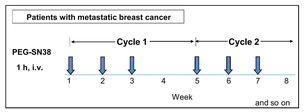
- Despite the numerous therapies available, there remains a need for new effective therapy for patients with previously-treated MBC
- EZN-2208 (polyethylene glycol [PEG]-SN38) is a water soluble PEGylated conjugate of SN38
- SN38 is the active metabolite of irinotecan (CPT-11, Camptosar) and has 100 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	8 (10%)	3 (4%)
Median age	56 (30–84)	55 (36–83)
Mean disease duration (yrs)	4.6	7.6
# Prior cytotoxic regimens for MBC		
≤ 2 regimens	79 (98%)	31 (37%)
> 2 regimens	2 (2%)	52 (63%)
Anthracycline (A)	80 (99%)	80 (96%)
Taxane (T)	81 (100%)	82 (99%)
Capecitabine (X)	0	83 (100%)
ECOG		
0	31 (38%)	29 (35%)
1	46 (57%)	50 (60%)
2	4 (5%)	4 (5%)
Receptor status		
ER+[1]	43 (54%)	58 (69%)
HER2+	8 (10%)	10 (12%)
Triple Negative	36 (44%)	21 (25%)

[1]ER+ in both AT and ATX includes 6 subjects who were also HER2+; Data as of April 23, 2012

Final Results

Treatment Exposure

- The median number of study treatment cycles was similar for both cohorts
  - AT: 4.0 (0.3–24.0+)
  - ATX: 3.0 (0.3–19.7+)

Efficacy

Primary and Secondary Endpoints			
Patients (n)		**AT**	**ATX**
Treated		81	83
Not Evaluable		9	8
Evaluable		72	75
Primary Endpoint		**n (%)**	
Overall	RR[1]	18[2] (25%)	8[3] (11%)
	Clinical Benefit	31 (43%)	22 (29%)
Secondary Endpoints			
Triple Negative	RR	8 (26%)	3 (19%)
	Clinical Benefit	10 (32%)	5 (31%)
ER+	RR	9 (24%)	5 (9%)
	Clinical Benefit	19 (50%)	17 (31%)
HER2+	RR	1 (17%)	0
	Clinical Benefit	2 (33%)	3 (30%)
		Months (95% CI)	
Median Duration of Response		5.6 (3.7–6.2)	8.8 (1.9–13.0)
Median PFS		3.8 (3.3–5.3)	3.5 (1.9–5.3)
Median OS		9.5 (8.8–12.4)	9.1 (7.5–13.3)
		Percent (95% CI)	
6-month PFS		33% (22%–43%)	26% (17%–36%)

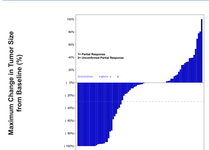
[1]RR = (PR+uPR); [2]16 PR, 2 unconfirmed PR; [3]7 PR, 1 unconfirmed PR; Data as of April 23, 2012

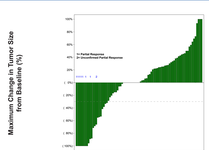
Clinical Benefit for Platinum Resistant Patients		
Platinum Progressor[1]		**n (%)**
Overall	Clinical Benefit	7 (18%)
Triple Negative	Clinical Benefit	4 (18%)

[1]Platinum Progressor = patient who progressed during or within 30 days of prior platinum-containing regimens; Data as of April 23, 2012

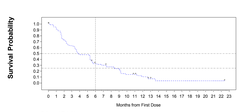
Figures **AT** **ATX**

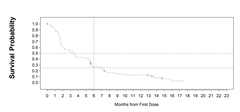
Maximum Change From Baseline





Progression Free Survival





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	4 (5%)		5 (6%)	
Diarrhea	4 (5%)		5 (6%)	
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	56 (69%)		42 (51%)	
Neutropenia	19 (24%)	18 (22%)	17 (21%)	12 (15%)
Diarrhea	11 (14%)	-	9 (11%)	-
Leukopenia	9 (11%)	3 (4%)	8 (10%)	-
Dehydration	5 (6%)	-	6 (7%)	-
Nausea	2 (3%)	-	6 (7%)	-
Fatigue	4 (5%)	-	4 (5%)	-

Data as of April 23, 2012

Conclusions

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

AT
- **25% RR (PR+uPR)**
- **33% 6-month PFS**

ATX
- **11% RR (PR+uPR)**
- **26% 6-month PFS**

- Significant activity was observed in many patient subsets including patients with triple-negative breast cancer **(AT: 26% RR, 32% clinical benefit; ATX: 19% RR, 31% 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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