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

EZN-2208 is a novel polyethylene glycol (PEG)-conjugated derivative of SN38 that provides advantages over SN38 and SN38G in terms of tumor selectivity, pharmacokinetics, and prevention of dose-limiting toxicities. This phase 2 study evaluated EZN-2208 in patients with hormone-refractory metastatic breast cancer (MBC), including patients who had progressed on prior platinum therapy. The primary objective was to evaluate the clinical benefit of EZN-2208 in this population. Secondary objectives included evaluation of overall clinical benefit, objective response rate (ORR) and duration of response (DOR), safety, and tolerability of EZN-2208 in patients who had progressed on prior platinum-containing regimens.

Background

EZN-2208 is a novel polyethylene glycol (PEG)-conjugated derivative of SN38 that provides advantages over SN38 and SN38G in terms of tumor selectivity, pharmacokinetics, and prevention of dose-limiting toxicities. This phase 2 study evaluated EZN-2208 in patients with hormone-refractory metastatic breast cancer (MBC), including patients who had progressed on prior platinum therapy. The primary objective was to evaluate the clinical benefit of EZN-2208 in this population. Secondary objectives included evaluation of overall clinical benefit, objective response rate (ORR) and duration of response (DOR), safety, and tolerability of EZN-2208 in patients who had progressed on prior platinum-containing regimens.

Objectives

- The primary objective was to determine the efficacy of EZN-2208 in patients with hormone-refractory metastatic breast cancer (MBC), including patients who had progressed on prior platinum therapy.
- Secondary objectives included evaluation of overall clinical benefit, objective response rate (ORR) and duration of response (DOR), safety, and tolerability of EZN-2208 in patients who had progressed on prior platinum-containing regimens.

Study Design

- Patients with metastatic breast cancer (MBC) who had progressed on prior platinum therapy or who were intolerant of prior platinum-containing therapy were eligible for enrolment. Patients were stratified into cohorts A (AT) and ATX (PEG-SN38) and were administered single-agent EZN-2208 for up to 12 months . The primary endpoint was overall clinical benefit (CR + PR + SD for ≥ 6 months).

Key eligibility criteria

- **Primary:**
  - MBC, with metastatic disease ($\geq$ 1 metastatic lesion).
  - Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
  - Progressive disease on prior therapy or intolerance of therapy.
  - Age $\geq$ 18 years.
  - Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.

- **Secondary:**
  - Total bilirubin within normal limits.
  - Serum creatinine $\leq$ 1.5 ULN or $\leq$ 2.5 ULN if creatinine clearance $\geq$ 50 ml/min.
  - Platelet count $\geq$ 100,000/mm$^3$.

- **Exclusion:**
  - Pregnancy or nursing (pregnant or lactating women are excluded).
  - Significant cardiac disease.
  - Active inflammatory bowel disease.
  - History of previous malignancy.

- **Inclusion:**
  - MBC.
  - Progression of disease on prior therapy or intolerance of therapy.

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  - Significant cardiac disease.
  - Active inflammatory bowel disease.
  - History of previous malignancy.

- **Inclusion:**
  - MBC.

Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AT</th>
<th>ATX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>56 (69%)</td>
<td>42 (51%)</td>
</tr>
<tr>
<td>ECOG</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Prior regimens</td>
<td>9 (12%)</td>
<td>8 (10%)</td>
</tr>
<tr>
<td>Metastases</td>
<td>3 (4%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Liver metastases</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Brain metastases</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Bone metastases</td>
<td>2 (3%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Other metastases</td>
<td>2 (3%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Prior cytotoxic therapies</td>
<td>2 (3%)</td>
<td>2 (3%)</td>
</tr>
</tbody>
</table>

Endpoints

- **Primary Endpoint:**
  - Overall clinical benefit: CR + PR + SD for ≥ 6 months.

- **Secondary Endpoints:**
  - Duration of response: Patients with CR or PR were included in the analysis of duration of response.
  - Safety: Adverse events were assessed using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0.

Results

- **Primary Endpoint:**
  - The clinical benefit rate (CBR) was 40% (10/25) for AT and 32% (8/25) for ATX.
  - The median duration of response was 8.8 (1.9–13.0) months for AT and 3.7 (1.6–6.2) months for ATX.

- **Safety:**
  - The safety profile of EZN-2208 was acceptable with good tolerability in most patients.
  - The most common adverse events were fatigue, diarrhea, and neutropenia.

Conclusions

- EZN-2208 is active in patients with previously treated metastatic breast cancer. The activity is similar in patients with triple negative breast cancer (TNBC) and in platinum pretreated patients.

References


