Poster 448

# A Phase 2 Study of EZN-2208 (PEG-SN38) Administered With or Without Cetuximab in Patients with Metastatic Colorectal Carcinoma (mCRC)

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RM Goldberg[1, 3], CR Garrett[2], N Berkowitz[9], T Bekaii-Saab[3], T Ryan[4], G Fisher[5], S Clive[6], P Kavan[7], E Shacham-Shmueli[8], A Buchbinder[9]

[1]Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC; [2]University of Texas M.D. Anderson Cancer Center, Houston, TX; [3]Ohio State University, Columbus, OH; [4]New York University Medical Center, NY, NY; [5]Stanford University Medical Center, Stanford, CA; [6]Edinburgh Cancer Centre, Edinburgh, UK; [7]Jewish General Hospital, Montreal, QC, Canada; [8]Tel Aviv Souraski Medical Center, Tel Aviv, Israel; [9]Enzon Pharmaceuticals, Inc., Piscataway, NJ

## Abstract

**Background:** EZN-2208 is a water-soluble, parenterally-delivered PEGylated conjugate of SN38 that increases solubility, exposure, and apparent half-life of SN-38. EZN-2208 has demonstrated anti-cancer activity in tumors with *K-RAS* mutation (Mut), in models of *in vivo*-induced irinotecan-resistant CRC, as well as various other clinical models giving it potential as a therapy in metastatic colorectal carcinoma (mCRC).

**Methods:** Patients with metastatic or locally recurrent CRC previously treated with fluoropyrimidines, oxaliplatin and irinotecan, progressing within 3 months of receiving these agents, and no more than 2 distinct progressions, were screened for *K-RAS* Mut and stratified accordingly. Patients with *K-RAS* Mut were treated with single agent EZN-2208 (9 mg/m$^2$ SN-38 equivalents) over 1-h IV on days 1, 8, 15 in 4-wk cycles (Arm A). Patients with *K-RAS* wild type (WT) tumors were randomized (2:1) to EZN-2208 (as above) and cetuximab (250 mg/m$^2$ weekly following 400 mg/m$^2$ on day 1) (Arm B) or to irinotecan (125 mg/m$^2$) over 90 min IV on days 1, 8 in 3-week cycles and cetuximab (as above) (Arm C). The primary objectives of the study were to determine the overall response rate (RR) in all Arms and determine the median progression free survival (PFS) in Arms B and C. Safety parameters are reported.

**Results:** RR in Arms A, B and C was 0%, 12.3% and 11.4%, respectively. PFS in Arm B was 3.7 (95% CI: 2.5, 5.4) months and in Arm C was 3.0 (95% CI: 1.9, 4.2) months.Median Overall Survival (OS) was 9.6 (95% CI: 8.3, 11.1) months in Arm B compared with 8.6 (95% CI: 5.2, 16.0) months in Arm C. Treatment exposure median, (range) in weeks was: Arm A, 8 (4-42); Arm B, 17 (3-84); Arm C, 12 (2-56). Drug related adverse events (AEs) seen in ≥ 25% of patients in the single agent arm were fatigue: 46%; neutropenia: 46%; diarrhea: 39%; nausea: 35%; anemia: 25%. AEs ≥ Grade 3 that were seen in ≥ 10% of patients in at least one arm in combination therapy—Arms B and C respectively—were: neutropenia: 34%, 16%; diarrhea: 19%, 21%; dehydration: 10%, 8%; abdominal pain 8%, 11%, and anemia: 1%, 11%. For all arms of the study, no single serious AE was observed in >10% of patients.

**Conclusions:** EZN-2208 in combination with cetuximab is active in patients in the third-line setting of CRC and comparable to irinotecan in combination with cetuximab. EZN-2208 monotherapy did not result in responses in patients with *K-RAS* Mut CRC who progressed within 3 months of irinotecan, oxaliplatin and 5FU therapy. EZN-2208 has an acceptable safety and tolerability profile as monotherapy, and in combination with cetuximab.

## Background

- Cetuximab is approved in combination with irinotecan in patients with EGFR-expressing metastatic colorectal carcinoma who are refractory to irinotecan-based chemotherapy. Approval is based on objective response rate. Use of cetuximab is not recommended for the treatment of patients with mCRC whose tumors had *K-RAS* mutations in codon 12 or 13[1]
- There is no approved therapy for patients with mCRC expressing *K-RAS* Mut who progress after therapy with irinotecan, oxaliplatin, and fluoropyrimidine
- The combination of cetuximab + irinotecan has a response rate approaching 0% in patients with *K-RAS* Mut expressing mCRC progressing after irinotecan therapy[2]
- EZN-2208 (polyethylene glycol [PEG]-SN38) is a water soluble, parenterally-delivered, PEGylated conjugate of SN38
- PEGylation of SN38 increases its solubility and half-life, yielding higher SN38 exposure in patients[3, 4]
- EZN-2208 properties of interest preclinically:
  - Compared with irinotecan – higher tumor exposure, longer half-life, more profound DNA damage and inhibition of angiogenesis[5, 6]
  - Preferential accumulation in tumors secondary to enhanced permeability and retention effect
  - Marked anti-cancer activity in CRC models of *in vivo*-induced resistance to irinotecan[5]
    - In the HT-29 colorectal cancer model, EZN-2208 showed marked antitumor activity in mice that failed CPT-11 treatment
  - Marked anti-cancer activity in tumors with *K-RAS* Mut (i.e., MiaPaCa-2 pancreatic, Calu6 lung, and SW480 colorectal models) and other preclinical models[5, 7]
- EZN-2208 has preclinical activity in models of irinotecan-resistant and refractory tumors and in models with WT and Mut *K-RAS*[9]
- Phase 1 dose-escalation studies in patients with advanced malignancies have shown EZN-2208 to be safe and well tolerated, with prolonged stable disease (SD), up to 1 year, in patients with mCRC previously treated with irinotecan[3, 4]

## Objectives

### Primary Objectives

- Determine overall response rate (RR) of EZN 2208 for two distinct cohorts of patients with mCRC
  - Patients with Mut *K-RAS* tumors (Arm A, Single agent EZN-2208)
  - Patients with WT *K-RAS* tumors (Arms B, EZN-2208 in combination with cetuximab; and Arm C, irinotecan in combination with cetuximab)
- Determine PFS for Arms B and C (WT *K-RAS* tumors):

### Secondary Objectives

- Evaluate duration of response (DOR) for each treatment arm
- Evaluate PFS for Arm A
- Evaluate OS and safety for each treatment arm
- Benchmark primary and secondary endpoints observed in Arm B with those observed in Arm C

## Study Design

- Phase 2, multicenter, multiple-arm, open-label study with enrollment from July 2009 to July 2011

### Key eligibility criteria:

- Progressive, histologically confirmed CRC adenocarcinoma that is metastatic or locally recurrent CRC that is nonresectable
- Previous therapy with irinotecan, oxaliplatin, and fluoropyrimidine either alone or in any combination(s)
- Radiographic-documented progressive disease while receiving, or within 3 months of receiving, these agents alone or in combination
- Age >18

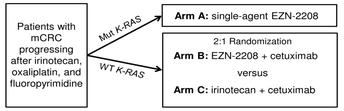
### Treatment

**Arm A:** EZN-2208 9 mg/m$^2$ administered weekly for 3 weeks in 4-week cycles

**Arm B:** EZN-2208 9 mg/m$^2$ administered weekly for 3 weeks in 4-week cycles + cetuximab 250 mg/m$^2$ administered weekly after a 400mg/m$^2$ loading dose

**Arm C:** Irinotecan 125 mg/m$^2$ administered weekly for 2 weeks in 3-week cycles + cetuximab 250 mg/m$^2$ administered weekly after a 400 mg/m$^2$ loading dose

- Tumors were tested for *K-RAS* status (Mut vs WT) for stratification




- Patients were evaluated every 2 cycles (approximately every 8 weeks)
- Objective tumor response was determined using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1[9]

## Demographics

| | Arm A: *K-RAS* Mut | Arms B & C: *K-RAS* WT | |
|---|---|---|---|
| | EZN-2208 | EZN-2208 + cetuximab | irinotecan + cetuximab |
| **Patients treated** | 93 | 80 | 38 |
| **Patients evaluable** | 80 (86%) | 73 (91%) | 35 (92%) |
| **Median age (range)** | 59 (21–81) | 62 (32–81) | 61 (35–72) |
| **Gender (male / female)** | 47% / 53% | 54% / 46% | 55% / 45% |
| **Median duration of disease (years)** | 2.1 | 1.9 | 2.3 |
| **Past response to irinotecan** | 3 (3%) | 13 (17%) | 3 (8%) |
| **Baseline ECOG** | | | |
| **0** | 37 (40%) | 35 (44%) | 16 (42%) |
| **1** | 54 (58%) | 45 (56%) | 22 ( 58%) |
| **2** | 2 (2%) | 0 | 0 |

Data as of November 28, 2011

## Results

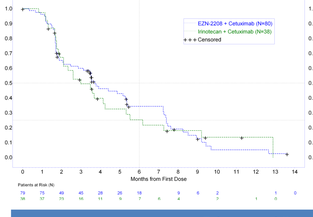
### Treatment Exposure

| | Arm A | Arms B & C | |
|---|---|---|---|
| | EZN-2208 | EZN-2208 + cetuximab | irinotecan + cetuximab |
| **Median # of treatment cycles** (min, max) | 2.0 (0.6, 9.8) | 4.0 (0.3, 20.9) | 3.5 (0.7, 18.7) |
| **Median duration drug exposure-wks** (min, max) | 8.0 (3.9, 41.9) | 17.1 (3.0, 83.7) | 12.1 (2.0, 56.0) |

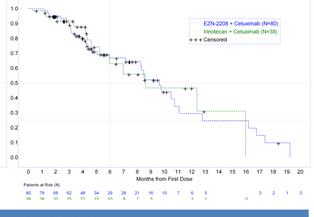
### Efficacy

- In Arm A, the RR was 0% with a median PFS of 1.8 months (95% CI: 1.7, 1.9)
  - 32 (40%) patients had a best response of stable disease, while 48 (60%) had a best response of progressive disease
- In Arms B and C the RR was 12.3% and 11.4% with a median PFS of 3.7 months (95% CI: 2.5, 5.4) and 3.0 months (95% CI: 1.9, 4.2) respectively
- OS for Arms B and C was 9.6 (95% CI: 8.3,11.1) and 8.6 (95% CI: 5.2,16.0) months respectively. However, 55% of patients in the Arm B and 66% of patients in Arm C were still alive at the time of this analysis.

### Progression Free Survival




### Overall Survival

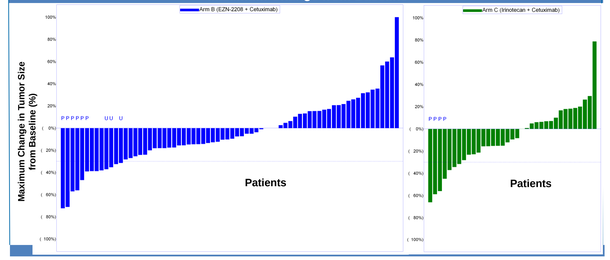



### Primary and Secondary Endpoints

| | Arm B | Arm C |
|---|---|---|
| **Patients (n)** | | |
| **Treated** | 80 | 38 |
| **Not Evaluable** | 7 | 3 |
| **Evaluable** | 73 | 35 |
| **Responders - n (%)*** | 9 (12.3%) | 4 (11.4%) |
| **Median duration of response, months (95% CI)** | 5.6 (1.8, 7.9) | 8.3 (2.5, 9.5) |
| **Median PFS, months (95% CI)** | 3.7 (2.5, 5.4) | 3.0 (1,.9, 4.2) |
| **Median OS, months (95% CI)** | 9.6 (8.3, 11.1) | 8.6 (5.2, 16.0) |
| **6-month PFS** | 34% (23%, 46%) | 25% (10%, 41%) |

*Responders = (PR+uPR); Arm B - 6 PR, 3 unconfirmed PR; Data as of November 28, 2011

### Maximum Change from Baseline




### Safety & Tolerability

- 9% of patients in **Arm A** received EZN-2208 for more than 6 months
- 26% of patients in **Arm B** received EZN-2208 for more than 6 months
- 21% of patients in **Arm C** received irinotecan for more than 6 months

| ADVERSE EVENTS Arm A | Arm A |
|---|---|
| **Serious AEs seen in ≥ 5% of patients** | |
| Dehydration | 5 (5%) |
| Vomiting | 3 (3%) |
| **Drug-related AEs seen in ≥ 5% of Patients** | |
| Any | 83 (89%) |
| Fatigue | 43 (46%) |
| Neutropenia | 43 (46%) |
| Diarrhea | 36 (39%) |
| Nausea | 33 (35%) |
| Anemia | 23 (25%) |
| Vomiting | 20 (22%) |
| Leukopenia | 14 (15%) |
| Anorexia | 12 (13%) |
| Alopecia | 10 (11%) |
| Constipation | 9 (10%) |
| Dysgeusia | 7 (8%) |
| Thrombocytopenia | 6 (6%) |
| Dehydration | 5 (5%) |
| Hypokalemia | 5 (5%) |
| White blood cell count decreased | 5 (5%) |

| ADVERSE EVENTS Arms B & C | Arm B | Arm C |
|---|---|---|
| **Serious AEs seen in ≥ 5% of patients** | | |
| Dehydration | 6 (8%) | 3 (8%) |
| Vomiting | 5 (6%) | 0 |
| **AEs ≥ Grade 3 seen in ≥ 10% of patients in at least 1 Arm** | | |
| Any* | 64 (80%) | 23 (61%) |
| Neutropenia | 27 (34%) | 6 (16%) |
| Diarrhea | 15 (19%) | 8 (21%) |
| Dehydration | 8 (10%) | 3 (8%) |
| Abdominal pain | 6 (8%) | 4 (11%) |
| Anemia | 1 (1%) | 4 (11%) |

*Patients with any Adverse Events- Grade 3 or higher; Data as of November 28, 2011

| Discontinuations | | | |
|---|---|---|---|
| **Reason for ending treatment** | **Arm A** | **Arm B** | **Arm C** |
| Adverse event | 6 (6%) | 4 (5%) | 1 (3%) |
| Progressive disease | 74 (80%) | 53 (66%) | 22 (58%) |
| Ongoing | 0 | 12 (15%) | 6 (16%) |

- There were no drug-related AEs leading to death

## Conclusions

- EZN-2208 in combination with cetuximab is active in patients in the third-line setting of CRC progressing within 3 months of irinotecan, oxaliplatin and 5-FU therapy, and comparable to irinotecan in combination with cetuximab
- EZN-2208 monotherapy did not result in responses in patients with *K-RAS* Mut mCRC following progression within 3 months of irinotecan, oxaliplatin and 5-FU therapy
- EZN-2208 has an acceptable safety and tolerability profile as monotherapy, and in combination with cetuximab

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