Etirinotecan pegol Target-Specific Pharmacodynamic (PD) Biomarkers Measured in Circulating Tumor Cells (CTCs) from Patients in the Phase 3 BEACON Study in Patients with Metastatic Breast Cancer (mBC)

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BACKGROUND

Enrollment of patients with locally recurrent or metastatic breast cancer in a randomized multicenter study of Etirinotecan pegol (NKTR-102) was completed. A phase II dose-escalation study in patients with metastatic breast cancer whose disease had failed prior taxane-based treatment, included patients assessed for the presence or absence of circulating tumor cells (CTCs) in peripheral blood. The number of CTCs or change in number of CTCs upon treatment potentially indicate increased repair of topoisomerase 1 inhibitor induced lesions.

METHODS

All 125 patients included in the BEACON mBC study were drawn and shipped ambient to ApoCell (Houston, TX) for further processing. Results from baseline (predose) samples are presented. PBMCs were separated and CTCs were isolated using the ApoStream system equipped with iCys 3.4.12 image analysis software. All assays were performed on an ApoAssay™ platform.

ASSAY DEVELOPMENT AND QUALIFICATION

Representative images of biomarkers on pre-dose CTCs isolated from BEACON Patients

METHODS

Biomarkers (Top 1, Top 2, Markers of DNA damage/apoptosis) measured in circulating tumor cells and tumor tissue (mechanism of action).

**Biomarkers**

- Top1+
- H2Ax+
- RAD51
- Ki67

CTC targets

**Top1** is a nuclear enzyme that plays a critical role in DNA replication, transcription, recombination and repair. Topoisomerase 1 inhibitors, such as SN38, the active metabolite of etirinotecan pegol, stabilizes the DNA-topoisomerase 1 complex subsequently restricting SN38 entry into brain.

**H2Ax** is a protein which becomes phosphorylated at serine 139 in response to DNA double-strand breaks. Patients with locally recurrent breast cancer previously treated with a taxane, as indicated by increased expression of H2Ax in circulating tumor cells (CTCs), demonstrated an overall survival benefit from etirinotecan pegol treatment.

**RAD51** is a recombinase protein that mediates strand exchange in double-strand break repair. Patients with locally recurrent breast cancer previously treated with a taxane, as indicated by increased expression of RAD51 in circulating tumor cells (CTCs), demonstrated an overall survival benefit from etirinotecan pegol treatment.

**Ki67** is a nuclear protein that is expressed in proliferating cells and is widely used as a proliferation marker. Patients with locally recurrent breast cancer previously treated with a taxane, as indicated by increased expression of Ki67 in circulating tumor cells (CTCs), demonstrated an overall survival benefit from etirinotecan pegol treatment.

**Pharmacodynamic (PD) Biomarkers**

CTC Target-Specific Pharmacodynamic (PD) Biomarkers Measured in Circulating Tumor Cells (CTCs) from Patients in the Phase 3 BEACON Study in Patients with Metastatic Breast Cancer (mBC)

INTRODUCTION

Resistance mechanisms described for topoisomerase 1 inhibitors include...

SN38, the active metabolite of Etirinotecan pegol, stabilizes the DNA-topoisomerase 1 complex subsequently restricting SN38 entry into brain.

**Background:**

- Topoisomerase 1 (Top1) is a nuclear enzyme that plays a critical role in DNA replication, transcription, recombination, and repair.
- SN38, the active metabolite of etirinotecan pegol, stabilizes the DNA-topoisomerase 1 complex subsequently restricting SN38 entry into brain.
- Resistance mechanisms described for topoisomerase 1 inhibitors include...
- SN38, the active metabolite of etirinotecan pegol, stabilizes the DNA-topoisomerase 1 complex subsequently restricting SN38 entry into brain.
- Increased expression of repair proteins.
- Increased repair of Top1 inhibitor induced lesions.
- Circulating tumor cells (CTCs) are an attractive minimally invasive alternative to tumor biopsies for clinical applications.

**Pre-Dose CTC Results**

**Target-Specific Biomarkers**

**Target-Specific Pharmacodynamic (PD) Biomarkers**

**Pharmacokinetic profile of etirinotecan pegol (NKTR-102)**: continuous exposure.

**ENROLLMENT:**

- **Assay Development and Qualification:**
  - Target-Specific Pharmacodynamic (PD) Biomarkers measured in circulating tumor cells and tumor tissue.

**CONCLUSIONS**

- **Biomarkers:**
  - ApoAssay™ technology was successfully incorporated into the BEACON study.
  - CTC laboratory patient participation was greater than 90%.
  - ApoAssay™ assesses CTCs in 100% of samples. Median number of CTCs is high.
  - Etirinotecan pegol target-specific pharmacodynamic biomarkers can be reliably measured in CTCs isolated from patients participating in BEACON and can be a potential predictive measure of clinical response.

**REFERENCES**

**1.** Lin et al., Clin. Cancer Res. 2013, 19(8), 2084–95.
**3.** Kluin-Nelemans JC, et al., Clin Cancer Res. 2007;13(17):5034–42.