**ABSTRACT**

Background: Cancer Stem Cells are considered to be fundamentally important for resistance to therapy, recurrence and metastasis. Napabucasin (also known as BMN 307 and BMN 310), a first-in-class cancer stemness inhibitor (in clinical development) was identified by its ability to inhibit OCT4-driven gene transcription and sphere formation of cancer stem cells only. (Li S. PNAS 2013;110(30)). Preclinical studies suggest that napabucasin sensitizes heterogeneous cancer cells to chemotherapy and targeted agents.

Methods: A phase I/II multicenter study in refractory PTX patients was performed to confirm the RRs, PFS profile and evidence of enhancement activity of napabucasin in combination with sub-PTX and gem. We enrolled napabucasin 200 mg or weekly sub-PTX 125 mg/m^2 and gem 1000 mg/m^2 for 3 out of every 4 weeks until disease progression (6 cycles).

Results: Of the 113 intent to treat (ITT) pts enrolled, 49 (44%) were treatment-relies and 17 (34%) received investigational treatment. There were no significant FK interactions, dose-limiting or unexpected toxicities. Most common adverse events (AEs) included grade 1 diarrhea, nausea, fatigue, mucositis, grade 2 alopecia, and grade 3 neutropenia. Napabucasin was not significantly added to or worsened the overall AEs profile of PTX and gem combination therapy (e.g., who met National Cancer Institute (NCI) criteria for Grade 4 enrollment, Grade 3 neutropenia, and Grade 2 neutropenia was 19% and 11% respectively). Treatment-related adverse events (TRAEs) with any grade of grade 3 or 4 were neutropenia (17.5%), diarrhea (12.5%) and nausea (10%). Among 64 ITT Pts. DCR was observed in 57 (79%), with 23 (36%) and 26 (40%) (ongoing, median progression free survival and overall survival) of ITT Pts. DCR at ITT was 35.1% in pts with LSM.

**OBJECTIVES:**

Primary:

- To determine the safety, tolerability and the recommended Phase II dose (RP2D) of napabucasin when administered in combination with sub-PTX and gem in adult pts with metastatic pancreatic cancer.

Secondary:

- To assess the pharmacokinetics and pharmacodynamics of napabucasin administered in combination with PTX and gem.

- To determine the pharmacokinetics (biomarker) of napabucasin administered in combination with sub-PTX and gem.

**STUDY DESIGN:**

- **Phase I:** Multiple dose, phase I study.
- **Continuous administration of napabucasin twice daily for 28 days cycle:**
- **2nd cycle:**

**DEFINITIONS:**

- **ORR:** Objective response rate.
- **DOR:** Duration of response.
- **PFS:** Progression-free survival.
- **OS:** Overall survival.
- **LMR:** Lymphocytes/monocytes ratio.
- **CR:** Complete response
- **PR:** Partial response
- **SD:** Stable disease
- **PD:** Progressive disease
- **ORR:** Objective response rate
- **DOR:** Duration of response
- **PFS:** Progression-free survival
- **OS:** Overall survival
- **LMR:** Lymphocytes/monocytes ratio
- **CR:** Complete response
- **PR:** Partial response
- **SD:** Stable disease
- **PD:** Progressive disease

**COMBINATION RATIONALES**

**Effect of Napabucasin and Gem Treatment on PDAC in Xenograft Tumor**

- **Napabucasin and gem therapy in vitro:**

**PATIENT POPULATION**

- **Of the 23 evaluable pts, disease control (CR+PR+SD) was observed in 15 (65 %) with 9 (39 %) CR and 6 (26 %) SD pts.**

**COMBINATION REGIONS SAFETY PROFILE**

- **Nausea:** 20% incidence in their CA 19-9 level.
- **Diabetes:** 13% reduction in their CA 19-9 level.
- **Hypokalemia:** 6% reduction in their CA 19-9 level.
- **Hypoglycemia:** 6% reduction in their CA 19-9 level.

**CONCLUSIONS:**

- Napabucasin at 240 mg QD 42 hours can be combined with navelitaxel (nab-PTX) and gem in full dose with no new AEs observed and no evidence of pharmacokinetics interaction noted.
- No evidence of AEs profile was observed in pts treated with nab-PTX and gem with napabucasin at 240 mg QD compared to nab-PTX and gem.
- Gastrointestinal AEs seen with nababucasin in combination with nab-PTX and gem were observed in a small number of pts.
- Encouraging anti-tumor activity was observed in pts with mPDAC, and is now being explored in a phase II study. Combined Data (2017): SF315, ASCO 2017 Abstract #K754148