CanStem111P Trial: A Phase III Study of Napabucasin plus nab-Paclitaxel (nab-PTX) with Gemcitabine (gem) in Adult Patients with Metastatic Pancreatic Adenocarcinoma (mPDAC)

Bekaii-Saab T[1,10], Goldstein D[2,10], Li CP[3,10], Okusaka T[4,10], O'Neil B[5,10], Reni M[6,10], Tabernero J[7,10], Qin S[8,10], Van Cutsem E[9,10], other CanStem111P Investigators[10], Borodyansky L[10,11] and Li CJ[10,12].

[1]Mayo Clinic Cancer Center, Scottsdale, AZ, USA; [2]Prince of Wales Hospital Clinical School, Sydney, Australia; [3]Taipei Veterans General Hospital, Taipei, Taiwan; [4]National Cancer Center, Tokyo, Japan; [5]IU Health University Hospital, Indianapolis, IN, USA; [6]IRCCS San Raffaele Scientific Institute, Milan, Italy; [7]Medical Oncology Department, Vall d'Hebron University Hospital and Institute of Oncology (VHIO), Barcelona, Spain; [8]Nanjing Bayi Hospital, Nanjing, China; [9]University Hospitals Gasthuisberg/Leuven, Leuven, Belgium; [10]Authorship was determined by alphabetical order of author last name; [11]Boston Biomedical, Inc., Cambridge, MA, USA; [12]1Globe Biomedical Co., Ltd., Beijing, China.

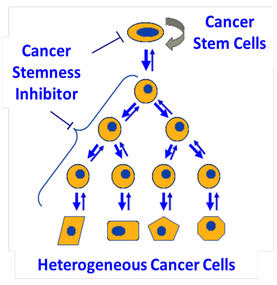
Background

Cancer Stem Cells (CSC)

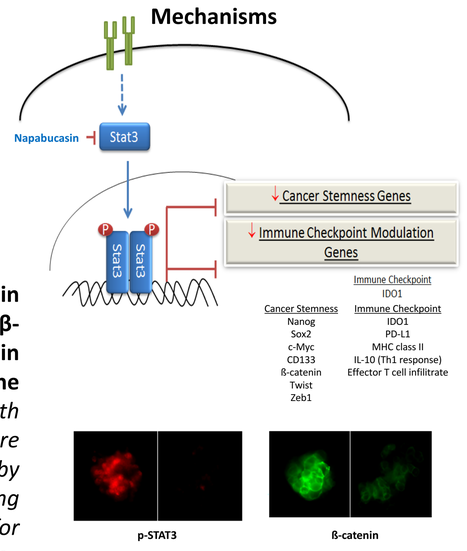
- Highly tumorigenic; fundamentally responsible for continued malignant growth, initiators (seeds) of metastases, and resistant to chemotherapy and current targeted therapies
- "Bulk" or non-CSCs induced toward stemness by chemotherapy exposure, priming chemotherapy refractory cancer for treatment with a CSC inhibitor
- Characteristic CSC cell surface markers including Lgr5, CD133, CD44, CD24, CD29, CD166, and Musashi-1

STAT3 and β-catenin in PDAC

- Elevated expression by IHC of p-STAT3 and nuclear β-catenin associated with advanced disease and poor outcome[1,2,3,4,5,6]
- Both STAT3 and β-catenin are important regulators of CSC-mediated self-renewal and survival in PDAC



Stat3 is a Key Driver of Cancer Stemness and Immune Evasion Mechanisms



Effect of Napabucasin Treatment on p-STAT3 and β-catenin Protein Levels in Human PDAC C12 Cell Line (Panc-1). *Cells treated with napabucasin or control were analyzed by immunofluorescence staining using antibodies specific for human p-STAT3 and β-catenin.*

Napabucasin (also known as BBI-608 and BBI608)[7]

- Orally administered first-in-class cancer stemness inhibitor
- Identified by its ability to inhibit STAT3-driven gene transcription and spherogenesis of cancer stem cells
- Mechanism of action is by inhibition of the STAT3 and Wnt/β-catenin pathways
- Preclinical studies suggest that napabucasin sensitizes heterogeneous cancer cells to chemotherapeutic agents, including nab-PTX + gem

Phase Ib Study[8,9]

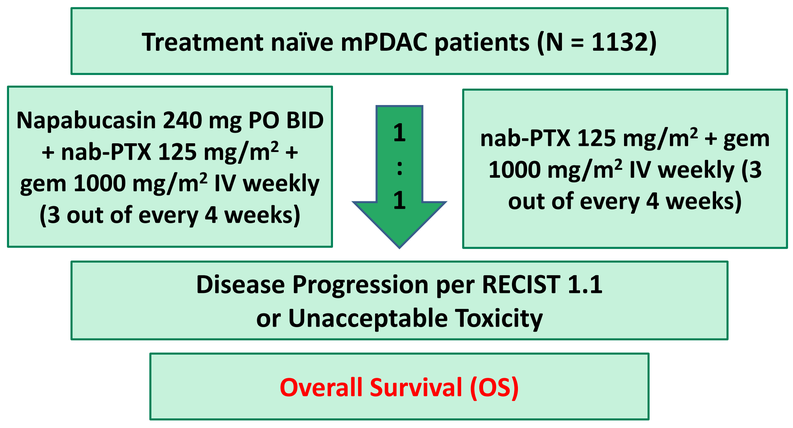
- ClinicalTrials.gov Identifier: NCT02231723
- Multi-center, open-label study of napabucasin continuous BID oral administered in combination with nab-PTX 125 mg/m^2 + gem 1000 mg/m^2 (3 out of every 4 weeks) in pts with mPDAC
- Encouraging anti-cancer activity from 66 pts presented at ASCO 2017. Among patients receiving RECIST evaluation (55):
  - 93% (51) disease control rate (DCR; CR+PR+SD)
  - 55% (30) overall response rate (ORR; CR+PR)
  - 2 complete (4%) and 28 (51%) partial responses
- Prolonged disease control (>24 wks) in 57% (17/30) of pts who have had a RECIST evaluation
- Adverse Event (AE) profile similar to that of both agents in monotherapy, with no new or additive effects observed
- No evidence of pharmacokinetic interaction
- RP2D of napabucasin determined as 240 mg BID

Registration and Support

- ClinicalTrials.gov Identifier: NCT02993731
- EudraCT Number: 2016-004359-57
- Supported by Boston Biomedical, Inc.

Aim & Study Schema

- This randomized, open-label study will assess the efficacy of napabucasin + nab-PTX + gem vs. nab-PTX + gem in pts with mPDAC



Endpoints

Primary

- OS in general study population

Secondary

- OS in predefined biomarker-positive sub-population¥
- Progression Free Survival (PFS) in general study population
- PFS in predefined biomarker-positive sub-population¥
- Objective Response Rate (ORR) in general study population
- Disease Control Rate (DCR) in general study population
- Safety Profile in general study population
- QoL in general study population

¥Pts with nuclear β-catenin and phospho-STAT3 positivity on IHC staining of archival tissue.

Eligibility *(abbreviated)*

Inclusion Criteria:

- Histologically or cytologically confirmed advanced PDAC that is metastatic
- Initial diagnosis of metastatic disease demonstrated ≤ 6 weeks prior to randomization
- Must not have received chemotherapy or any investigational agent for the treatment of mPDAC
  - A fluouropyrimidine or gemcitabine administered as a radiation sensitizer in the adjuvant setting allowed for as long as last dose was administered ≥ 6 months prior to randomization and no lingering toxicities present
- Appropriate for nab-PTX + gem therapy
- ECOG PS 0 or 1
- Life expectancy of > 12 weeks
- Age ≥ 18 years
- Contraception; negative pregnancy testing (WOCBP)
- One or more metastatic tumors evaluable by CT/MRI
- Hemoglobin ≥ 9.0 g/dL, Neutrophils ≥ 1.5 x 10^9/L, Platelets ≥ 100 x 10^9/L
- Alanine transaminase ≤ 2.5 × ULN [≤ 5 × ULN if liver metastases]
- Total bilirubin ≤ ULN
- Creatinine ≤ ULN or Creatinine Clearance > 60 ml/min
- PT/PTT within 15% of normal limits
- BMI ≥ 18kg/m^2, body weight > 40 kg, serum albumin ≥ 3 g/dL
- Consent to provision of tumor and blood samples
- Accessible for treatment and follow-up

Exclusion Criteria:

- No evidence of metastatic disease or local recurrence following surgical resection of primary lesions
- Decline in ECOG PS and albumin between Baseline visit and within 72 hours prior to randomization
- Any prior anti-cancer chemotherapy, biologic or investigational therapy
- Major surgery within 4 weeks
- Known brain of leptomeningeal metastases
- Clinically significant ascites
- Women who are pregnant or breastfeeding
- Gastrointestinal disorders which would significantly impede absorption of an oral agent
- Unable or unwilling to swallow napabucasin/PBO capsules
- Uncontrolled intercurrent illness, situation or geography that would limit compliance with study requirements
- Known hypersensitivity to gemcitabine, taxanes or any of their excipients
- Pts being treated with Warfarin
- History of other malignancies (except treated non-melanoma skin cancer, Cis cervix, or solid tumour DFS ≥ 5 years)

Treatment

- Pts will be randomized in a 1:1 ratio to receive napabucasin 240 mg twice daily continuously in combination with nab-PTX and gem, or nab-PTX and gem alone
- Treatment will continue until disease progression, death, intolerable toxicity, or patient/investigator decision to stop
- Disease assessment q8w (per RECIST 1.1)

Statistical Design

- Analysis will be according to randomized group, stratified by:
  - Geographical Region (North America/Western Europe/Australia vs. Japan/Korea vs. Rest of the World)
  - ECOG Performance Status (0 vs. 1)
  - Presence of liver metastases (yes vs. no)

Sample Size Calculation

- Power of 90% and a two-sided alpha of 5% to detect a 20% reduction in the continuous risk of death (HR 0.80, corresponding to an increase of median survival from 8.5 to 10.63 months)
- 864 events required to detect this reduction, which would be observed by randomizing 1132 pts over 24 months, following for an additional 12 months

Correlative Studies

- Analysis of archival tissue for predictive biomarkers
- Analysis of blood and plasma for predictive and pharmacodynamic biomarkers
- Population pharmacokinetics
- QOL questionnaire

Study Status

- The study is currently active in ~10% of selected sites and recruitment continues since enrollment of the first patient in December 2016.

References

1. Zhang Y et al. (2013). Canonical Wnt Signaling Is Required for Pancreatic Carcinogenesis. *Cancer Research*,73(15), 4909-4922.
2. Denley S et al. (2013). Activation of the IL-6R/Jak/Stat Pathway is Associated with a Poor Outcome in Resected Pancreatic Ductal Adenocarcinoma. *Journal of Gastrointestinal Surgery*, 17(5), 887-898.
3. Pramanik KC et al. (2015). Inhibition of β-catenin signaling suppresses pancreatic tumor growth by disrupting nuclear β-catenin/TCF-1 complex: critical role of STAT-3. *Oncotarget*, 6(13), 11561.
4. Scholz A et al. (2003). Activated signal transducer and activator of transcription 3 (STAT3) supports the malignant phenotype of human pancreatic cancer. *Gastroenterology,* 125(3), 891-905.
5. Fofaria NM & Srivastava SK (2014). STAT3 induces anoikis resistance, promotes cell invasion and metastatic potential in pancreatic cancer cells. *Carcinogenesis*, bgu233.
6. Fukuda A et al. (2011). Stat3 and MMP7 Contribute to Pancreatic Ductal Adenocarcinoma Initiation and Progression. *Cancer Cell,* 19(4), 441-455.
7. Li Y et al. (2015). Suppression of cancer relapse and metastasis by inhibiting cancer stemness. *PNAS,* 112(6):1839-1844.
8. El-Rayes B et al. (2016). A Phase Ib extension study of cancer stemness inhibitor BB608 (Napabucasin) in combination with Gemcitabine and nab-Paclitaxel (nab-PTX) in patients (pts) with metastatic pancreatic cancer. ASCO abstr.
9. Bekaii-Saab et al. (2017). A phase Ib/II study of cancer stemness inhibitor napabucasin (BBI-608) in combination with gemcitabine (gem) and nab-paclitaxel (nab-PTX) in metastatic pancreatic adenocarcinoma (mPDAC) patients (pts). ASCO asbtr.