The BRIGHTER trial: A phase III randomized double-blind study of napabucasin (BBI-608) + weekly paclitaxel versus placebo (PBO) + weekly paclitaxel in patients (pts) with pretreated advanced gastric and gastro-esophageal junction (GEJ) adenocarcinoma

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Background
Cancer Stem Cells (CSC)
- Highly tumorigenic
- Fundamentally responsible for continued malignant growth
- Initiators (seeds) of metasteses
- Resistant to chemotherapy and current targeted therapies

Napabucasin (also known as BBI-608 and BBIBP68) 1
- Orally-administered first-in-class cancer stemness inhibitor
- Blocks CSC self-renewal and induces cell death in CSCs as well as non-stem cancer cells

Pre-clinical
- Mechanism of action is by inhibition of the STAT3 and Wnt/beta-catenin pathways
- Blockade of CD44+/CD133+ sphere formation with napabucasin surpasses blockade by chemotherapeutics and biologics tested2
- p-STAT3 and beta-catenin protein expression inhibited in human colon cancer (SW480) xenograft nude mouse model after treatment with napabucasin

Phase Ib/II Study3
- Multi-center, open-label, dose escalation study of napabucasin administered in combination with weekly paclitaxel at 80 mg/m2 in pts with advanced solid tumors
- Napabucasin administered with continuous BID oral administration with multiple 4 week cycles
- Paclitaxel administered IV weekly on Days 1, 7 and 14 of each 4 week cycle
- 5 pts with gastric/GEJ adenocarcinoma enrolled and all 5 responded to treatment
- 3 pts had tumor regression (45%, 48%, 24%)
- 2 pts who failed prior taxane had prolonged stable disease (> 5 months)
- Ongoing gastric/GEJ cohort with 39 gastric or GEJ adenocarcinoma pts enrolled with encouraging signs of anti-cancer activity being positively confirmed.

Adverse Event (AE) profile similar to that of both agents in monotherapy, with no new or additive effects observed. Most common AEs:
- Gr 1-2 diarrhea, nausea, anorexia and fatigue
- Gr 3 events: reversible diarrhea (18%), abdominal pain (4%), nausea (1%), vomiting (3%), fatigue (6%) and dehydration (2%)
- RP2D of napabucasin determined as full monotherapy dose

Japanese Phase I Study3
- Open-label, study of napabucasin administered in combination with weekly paclitaxel at 80 mg/m2 in 6 pts with gastric and GEJ adenocarcinoma with response rate of 33.3% (2 out 6 pts), with 1 pt maintaining response > 7.5 months

Aim
This randomized, double-blind, PBO-controlled study will assess the efficacy and safety of napabucasin + paclitaxel versus PBO + paclitaxel in pts with pre-treated, advanced gastric and GEJ adenocarcinoma

Study Schema

Advanced Gastric and GEJ Adenocarcinoma Progressed on First Line Metastatic Therapy (N = 700)

Napabucasin 480 mg PO BID + paclitaxel 80 mg/m2 IV weekly (3 out of every 4 weeks)
PBO PO BID + paclitaxel 80 mg/m2 IV weekly (3 out of every 4 weeks)

Disease Progression per RECIST 1.1 or Unacceptable Toxicity

Overall Survival (OS)

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

Eligibility (abbreviated)

Inclusion Criteria:
- Histologically or cytologically confirmed metastatic or locally advanced and unresectable gastric or GEJ adenocarcinoma
- Appropriate for paclitaxel therapy
- Failed treatment with prior 1st line regimen containing at least a platinum/fluoropyrimidine doublet in the unresectable or metastatic disease setting with progression of disease during treatment or ≤ 6 months after last dose of treatment
- Concomitant treatment with anthracycline or anti-HER2 therapy allowed
- Taxane therapy in neo/adjuvant setting included as long as progression occurred > 6 months following completion of treatment
- ECOG PS 0 or 1
- Age ≥ 18 years
- Contraception; negative pregnancy testing (WOCBP)
- Hemoglobin ≥ 9.0 g/dL
- Neutrophils ≥ 1.5 × 109/L
- Platelets ≥ 100 × 109/L
- Total bilirubin ≤ 1.5 × ULN [≤ 2.0 x ULN if liver metastases]
- Alanine transaminase ≤ 3 × ULN [≤ 5 × ULN if liver metastases]
- Creatinine ≤ 1.5 × ULN or Creatinine Clearance > 50 ml/min
- Consent to tumour + blood sample banking
- Able and willing to complete QOL questionnaires

Exclusion Criteria:
- Anti-cancer therapy within the lesser of the usual cycle length of the prior regimen (a minimum of 10 days must be observed for oral fluoropyrimidines)
- Radiotherapy, immunotherapy, or investigational agents within 4 weeks (14 days for single palliative dose of RT ≤ 8 Gy)
- Pts who received taxane therapy in 1st line metastatic setting excluded
- Major surgery within 4 weeks
- Symptomatic brain metastases requiring steroids
- 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
- History of other malignancies (except treated non-melanoma skin cancer, Cis cervix, or solid tumour DFS ≥ 5 years)
- Prior treatment with paclitaxel

Treatment
- Pts will be randomized in a 1:1 ratio to receive napabucasin 480 mg or matching PBO twice daily continuously
- 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 (Asia vs North America, Europe, and Australia vs South America)
  - Time to progression on first line therapy (<6 months vs. 26 months from start of first line therapy)
  - Disease measurability by RECIST 1.1 (measurable disease present vs not present)
- Prior taxane therapy (yes vs no)

Sample Size Calculation
- Power of 90% and a two-sided alpha of 5% to detect a 24% reduction in the continous risk of death (HR 0.76, corresponding to an increase of median survival from 7.36 to 9.67 months)
- 566 events required to detect this reduction, which would be observed by randomizing 700 pts over 24 months, following for an additional 12 months

Interim Analysis
- Performed on OS (stratified log rank), when > 2/3rds (380) events observed:
  - H0: survival on napabucasin + paclitaxel ≤ survival on PBO + paclitaxel
  - H1: survival on napabucasin + paclitaxel > survival on PBO + paclitaxel
- If p ≤ 0.005, H0 rejected, napabucasin superiority declared early
- If p > 0.005, H1 rejected, napabucasin superiority not declared, and accrual continued to final analysis for OS

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
- As of February 2016, 364 pts were randomized
- Study continues to recruit pts

Registration and Support
- ClinicalTrials.gov Identifier: NCT02178956
- EudraCT Number: 2014-000774-18
- Supported by Boston Biomedical, Inc.

References