CanStem303C Trial: A Phase III Study of Napabucasin in Combination with 5-Fluorouracil (5-FU), Leucovorin, Irinotecan (FOLFIRI) in Adult Patients with Previously Treated Metastatic Colorectal Cancer (mCRC).

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Background

Cancer Stem Cells (CSC) and Cancer Stemness

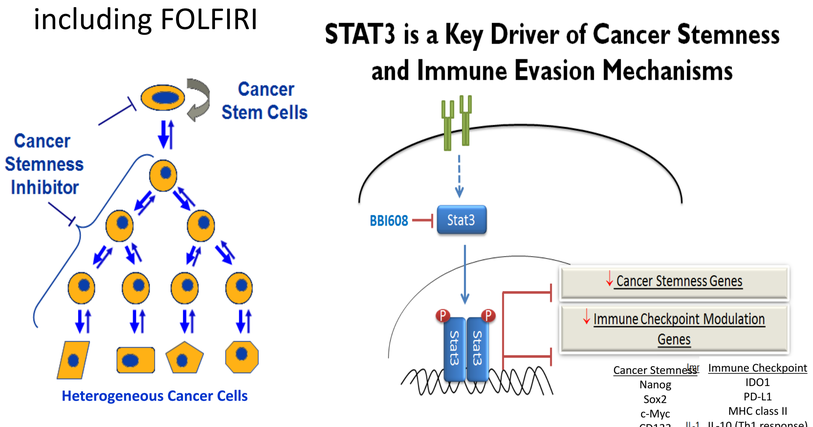
- Highly tumorigenic; fundamentally responsible for continued malignant growth, initiators (seeds) of metastases, and resistant to chemotherapy and current targeted therapies
- "Bulk" or non-CSCs induced toward stemness by chemotherapy exposure, priming chemotherapy refractory cancer for treatment with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

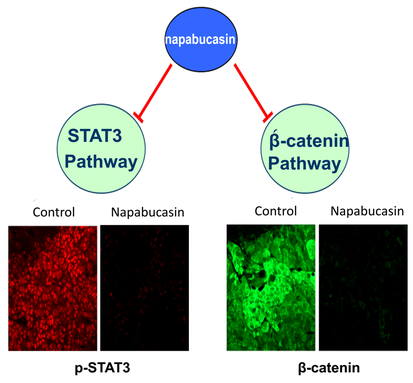
STAT3 and β-catenin in Colorectal Cancer

- Elevated expression by IHC of p-STAT3 and nuclear β-catenin associated with advanced disease and decreased survival in CRC and other GI cancers[1,2,3,4,5,6]
- Both STAT3 and WNT/β-catenin are important regulators of CSC-mediated self-renewal and survival in colorectal adenocarcinoma

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 FOLFIRI





Effect of Napabucasin Treatment on p-STAT3 and β-catenin Protein Levels in Human Colon Cancer Xenograft Tumor (SW480) in Nude Mice. *Formaldehyde-fixed tumors from mice treated daily for 15 days with oral gavage of Napabucasin or Vehicle (Control) were sectioned and analyzed by immunofluorescence staining using antibodies specific for human p-STAT3 and β-catenin.*

Phase Ib Study[8]

- Multi-center, open-label, extension study of napabucasin 240 mg PO BID administered in combination with bi-weekly FOLFIRI (5-FU 400 mg/m^2 bolus with 2400 mg/m^2, irinotecan 180 mg/m^2, and leucovorin 400 mg/m^2 infusion) +/- bev 5 mg/kg, in pts with advanced CRC
- 63 pts with CRC who failed an average of > 2 prior lines of therapy were enrolled, including 29 (46%) previously treated with FOLFIRI +/- bev.
- Among 56 pts enrolled who received RECIST 1.1 evaluation, DCR (PR+SD) was observed in 49 pts (88%) with an overall response (CR+PR) of 29% (16 pts), with 1 pt achieving CR. Among all pts enrolled, 33 pts (52%) had durable response to treatment.
- Ongoing CRC cohort being enrolled with encouraging signs of anti-cancer activity being positively confirmed.
- Most common adverse events (AEs) included grade 1/2 diarrhea, nausea, vomiting, anorexia and fatigue. 1 pt had grade 4 diarrhea and 27 pts had grade 3 AEs, including diarrhea (14), fatigue (4), dehydration (2), electrolyte imbalance (4), nausea (1), vomiting (1), abdominal pain (1) and weight loss (1), all of which resolved with dose reduction and supportive care
- No evidence of pharmacokinetic interaction

Aim

This randomized, open-label, study will assess the efficacy and safety of napabucasin + FOLFIRI versus FOLFIRI in pts with pre-treated, metastatic CRC.

Study Schema and Treatment

mCRC Patients Progressed on FOLFOX or CAPOX (with Bev if appropriate) Therapy (N = 1250)

Napabucasin 240 mg PO BID + standard FOLFIRI IV biweekly (bev 5 mg/kg per Investigator choice will be permissible)

1:1

Standard FOLFIRI IV biweekly (bev 5 mg/kg per Investigator choice will be permissible)

Disease Progression per RECIST 1.1 or Unacceptable Toxicity

Overall Survival (OS)

- Pts will be randomized in a 1:1 ratio to receive napabucasin 240 twice daily with standard biweekly FOLFIRI or standard biweekly FOLFIRI alone
- Addition of bev to the FOLFIRI regimen, per Investigator choice, will be permissible
- Treatment will continue until disease progression, death, intolerable toxicity, or patient/investigator decision to stop
- Disease assessment q8w (per RECIST 1.1) until 6 months and q12w thereafter

Eligibility *(abbreviated)*

Inclusion Criteria:

- Histologically confirmed metastatic CRC
- Appropriate for FOLFIRI therapy
- Failed treatment with one regimen containing a fluoropyrimide, oxaliplatin with or without bevacizumab for metastatic disease with a minimum 6 weeks treatment.
- No additional prior lines of therapy in the metastatic setting will be allowed
- Prior neoadjuvant or adjuvant treatment is allowed if no more than 2 prior systemic regimens were administered with no more than 1 prior regimen in the metastatic setting, with progression of disease occurring > 6 months from last dose of neoadjuvant or adjuvant treatment.
- For pts with rectal cancer, sequential neoadjuvant and adjuvant therapy will count as 1 regimen.
- Oxaliplatin rechallenge permitted and considered part of the first-line regimen for metastatic disease.
- ECOG PS 0 or 1; Age ≥ 18 years; contraception
- Adequate end-organ function: Hb ≥ 9.0 g/dL, WBC ≥ 1.5 x 10^9/L, plt ≥ 100 x 10^9/L, Total bili ≤ 1.5 × ULN [≤ 2.0 x ULN if liver metastases], ALT ≤ 3 × ULN [≤ 5 × ULN if liver metastases], Creatinine ≤ 1.5 × ULN or Creatinine Clearance > 50 ml/min

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 ≤ 4 weeks (14 days for single palliative dose of RT ≤ 8 Gy)
- Major surgery within 4 weeks
- Known brain or leptomeningeal metastases
- Women who are pregnant or breastfeeding
- Gastrointestinal disorders which would significantly impede absorption of an oral agent
- 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)

Correlative Studies

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

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) and disease control rate (DCR) in general study population
- ORR and DCR in biomarker-positive sub-population¥
- Safety profile in general study population
- Quality of life in general study population

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

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)
  - Time to progression from start of first line therapy (<6 months vs ≥6 months from start of first line therapy)
  - RAS mutation status (mutant vs wild type)
  - Bevacizumab as part of their protocol treatment (yes vs no)
  - Location of the primary tumor (left vs right colon)

Sample Size Calculation

- Power of 90% and a one-sided alpha of 0.025 to detect a 20% reduction in the continuous risk of death (HR 0.80, corresponding to an increase of median survival from 12.54 to 15.68 months)
- 850 events required to detect this reduction, which would be observed by randomizing 1250 pts over 26 months, following for an additional 11 months

Study Status and Information

- As of June 2017, study is activated in over 50% of selected sites and enrollment is ongoing with over 10% of patients enrolled.
- ClinicalTrials.gov Identifier: NCT02753127
- EudraCT Number: 2016-001627-31

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