BBI608-246: A phase Ib extension study of cancer stemness inhibitor napabucasin (BBI-608) administered in combination with FOLFIRI with and without bevacizumab (bev) in patients (pts) with advanced colorectal cancer (CRC)

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ABSTRACT

Background:

Napabucasin (BBI-608) is an oral first-in-class cancer stemness inhibitor targeting STAT3-driven gene transcription. Anti-tumor activity was observed *in vitro* and *in vivo*. Napabucasin showed clinical safety and encouraging signs of anti-cancer activity in multiple cancer types in phase I/II studies.

Methods:

A phase Ib extension multi-center study in pts with advanced CRC was undertaken to confirm the RP2D and signs of anti-cancer activity of napabucasin in combination with FOLFIRI +/- bev. Napabucasin was administered continuously at 240 mg BID in combination with 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, administered bi-weekly until disease progression, unacceptable toxicity, or other discontinuation criterion.

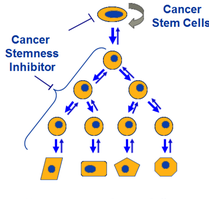
Results:

46 pretreated CRC pts who had failed an average of >2 prior lines of therapy were enrolled; including 21 pts (46%) previously progressed on FOLFIRI +/- bev. Of the 46 pts, 14 received napabucasin with FOLFIRI and 32 received napabucasin with FOLFIRI and bev. There was no dose-limiting or unexpected toxicity or significant pharmacokinetic interactions. Most common adverse events (AEs) included grade 1/2 diarrhea, nausea, vomiting and fatigue. Grade 3 AEs observed in 15 pts included diarrhea (10), fatigue (3), dehydration (1), hyponatremia (1), hypokalemia (1) and burning in rectum (1) resolved with dose reduction and/or supportive care. Disease control (PR+SD) was observed in 37 of 40 evaluable pts (93%), with partial response (PR) in 13 pts (33%) (33-67% regression), and stable disease with tumor regression in 18 pts (45%). Among 20 pts who had progressed on FOLFIRI +/- bev previously and were evaluable for tumor assessment, disease control (PR+SD) was observed in 18 pts (90%), tumor regression was observed in 15 pts (75%) of which 6 pts achieved PR (30%).

Conclusions:

This phase Ib extension study confirmed that napabucasin was safely combined with FOLFIRI +/- bev, and demonstrated encouraging signs of anti-tumor activity in CRC pts, including pts who had previously progressed on FOLFIRI +/- bev.

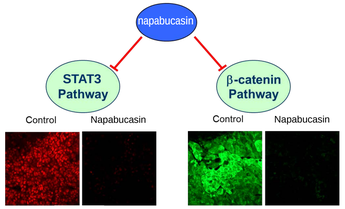
BACKGROUND



Cancer Stem Cells (CSC) and Cancer Stemness

- Highly tumorigenic
- Fundamentally responsible for continued malignant growth
- Initiators (seeds) of metastases
- Resistant to chemotherapy and current targeted therapies

Napabucasin is a *first-in-class* Cancer Stemness Inhibitor

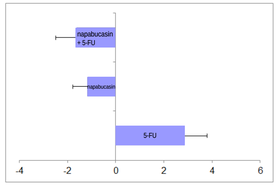


Effect of Napabucasin Treatment on p-STAT3 and β-catenin Protein Levels in Human Colon Cancer Xenograft Tumor (SW480) in Nude Mice. *Formaldehyde-fixed tumors from mice treated daily for 15 days with oral gavage of Napabucasin or Vehicle (Control) were sectioned and analyzed by immunofluorescence staining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

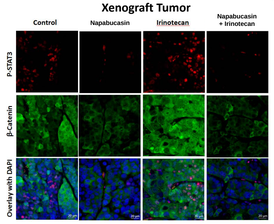
COMBINATION RATIONALE

- The combination of napabucasin with 5-FU and irinotecan showed strong synergy *in vitro* and *in vivo.*

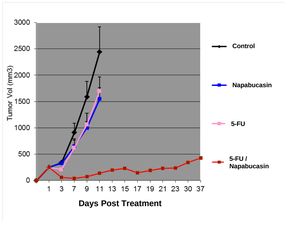
Effect of Treatments on Cancer Stem Cells



Effect of Treatments on Cancer Stemness Biomarker Response in Xenograft Tumor

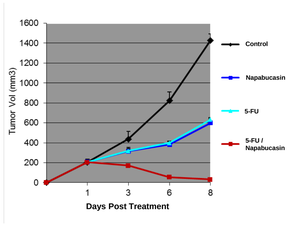


Synergistic Effect on Syngeneic Model of Colon Cancer (SW-480)



Six-week old female nude (NCR/nu) mice were injected S.C. with SW480 (10 x 10^6 cells). After 1 week (average tumor size 200-250 mm^3) mice were treated for 11 days with: PBS control, napabucasin (P.O. 100 mg/kg bid), 5-FU (I.P. 40 mg/kg q2d), and their combination. Each group consisted of 5 mice. Tumor volumes were measured three times a week.

Synergistic Effect on Syngeneic Model of Colon Cancer (CT-26)



Six-week old female Balb/c mice were injected S.C. with CT26 (3 x 10^5 cells). After 1 week (average tumor size 180-210 mm^3) mice were treated for 12 days with: PBS control, napabucasin (P.O. 50 mg/kg bid), 5-FU (I.P. 40 mg/kg q4d), and their combination. Each group consisted of 5 mice. Tumor volumes were measured three times a week.

OBJECTIVES

Primary:

- To determine the safety, tolerability and preliminary anti-tumor activity of napabucasin when administered in combination with FOLFIRI with and without bev in adult pts with advanced CRC.

Secondary:

- To assess the preliminary anti-tumor activity of napabucasin administered in combination with FOLFIRI with and without bev.
- To determine the pharmacokinetic profile of napabucasin administered in combination with FOLFIRI with and without bev.
- To determine the pharmacodynamics (biomarkers) of napabucasin administered in combination with FOLFIRI with and without bev.

STUDY DESIGN

- Open label, multi-center, phase Ib study
- Continuous oral administration of napabucasin twice daily in 28 day cycles
- Standard FOLFIRI regimen administered with or without bev every 14 days
- Objective tumor response assessed every 8 weeks using RECIST 1.1
- Pharmacokinetics and pharmacodynamics were evaluated

PATIENT POPULATION

- Histologically confirmed advanced CRC that is metastatic, unresectable, or recurrent and for which FOLFIRI with or without bev in combination with napabucasin is an acceptable therapeutic option
- Pre-treated with standard chemotherapy
- Karnofsky performance status ≥ 70% & adequate bone marrow, hepatic, and renal function

Baseline Demographics & Laboratory Values

N = 46

	N	%
Number of Prior		
0-2 prior	29	63%
≥ 3 prior	17	37%
Age		
Median	59	yrs
Range	40 – 73	yrs
Gender	N	%
Female	19	41%
Male	27	59%
Race	N	%
Caucasian	40	87%
Black	3	7%
Asian	2	4%
Other	1	2%
Karnofsky	N	%
100%	10	22%
90%	25	54%
80%	8	17%
70%	3	7%
K-Ras Status	N	%
WT	16	35%
Mutant	17	37%
N/A	13	28%

Hemoglobin		
Median	12.6	g/dL
Range	10.0-16.5	g/dL
Neutrophils		
Median	4.1	10^9/L
Range	1.9-12.4	10^9/L
Platelets		
Median	197.5	10^9/L
Range	105-579	10^9/L
ALT		
Median	28.5	U/L
Range	11-107	U/L
AST		
Median	28	U/L
Range	14-115	U/L
Creatinine		
Median	0. 8	mg/dL
Range	0.4-1.5	mg/dL

COMBINATION REGIMEN SAFETY PROFILE

- The combination of napabucasin and FOLFIRI with or without bev was well tolerated with no new adverse events observed beyond what is anticipated with FOLFIRI with or without bev
- The majority of adverse events observed were Grade 1 or 2 gastrointestinal adverse events
- Gastrointestinal adverse events observed with combination of napabucasin and FOLFIRI with or without bev were rapidly reversible and manageable with anti-diarrheals and anti-emetic supportive medications
- Napabucasin (240 mg BID q12 hours) was safely combined with bi-weekly FOLFIRI with or without bev at full doses
- No evidence of significant pharmacokinetic interactions was noted

Adverse Events (possibly/probably/definitely related to Napabucasin + FOLFIRI with or without Bev)*

Number and Percent of Total Subjects with a given Adverse Event by Grade

N = 40**

Organ System	Event	Grade 1 #	Grade 1 %	Grade 2 #	Grade 2 %	Grade 3 #	Grade 3 %
Gastrointestinal	Diarrhea	34	85.0%	21	52.5%	10	25.0%
	Nausea	30	75.0%	12	30.0%	0	0.0%
	Vomiting	20	50.0%	7	17.5%	0	0.0%
	Abdominal Pain	13	32.5%	8	20.0%	0	0.0%
	Mucositis	15	37.5%	4	10.0%	0	0.0%
	Flatulence	4	10.0%	1	2.5%	0	0.0%
	Dyspepsia	2	5.0%	3	7.5%	0	0.0%
Constitutional	Fatigue	26	65.0%	18	45.0%	3	7.5%
	Weight Loss	5	12.5%	2	5.0%	0	0.0%
Metabolism And Nutrition	Anorexia	17	42.5%	6	15.0%	0	0.0%
	Hypokalemia	2	5.0%	2	5.0%	1	2.5%
	Dehydration	0	0.0%	1	2.5%	1	2.5%
	Hyponatremia	0	0.0%	0	0.0%	1	2.5%
Skin And Subcutaneous Tissue	Alopecia	18	45.0%	9	22.5%	0	0.0%
Hematologic	Neutropenia	3	7.5%	11	27.5%	7	17.5%
	Urine Discoloration	8	20.0%	0	0.0%	0	0.0%
Neuro-Psychiatric	Dysgeusia	7	17.5%	1	2.5%	0	0.0%
	Headache	3	7.5%	2	5.0%	0	0.0%
	Insomnia	2	5.0%	4	10.0%	0	0.0%
Musculoskeletal Tissue	Myalgia	1	2.5%	3	7.5%	0	0.0%
Other	Burning Sensation in Rectum	1	2.5%	0	0.0%	1	2.5%

*Selection shown (any grade ≥10% and any with grade 3 events)

**AE data was available for 40 out of 46 patients at time of clinical cut-off for abstract submission

FOLFIRI alone was reported have diarrhea of Grade 1&2 in 42% , of Grade 3 in 8% and of Grade 4 in 1%; fatigue of Grade 1&2 in 44%, of Grade 3 in 8%; abdominal pain of Grade 1&2 in 18%, Grade 3 in 4%; nausea of Grade 1&2 in 47%, Grade 3 in 3%; vomiting of Grade 1&2 in 25%, Grade 3 in 3%. (Tabernero J, et al. 2015. Lancet Onc 16:499.)

SIGNS OF ANTI-CANCER ACTIVITY

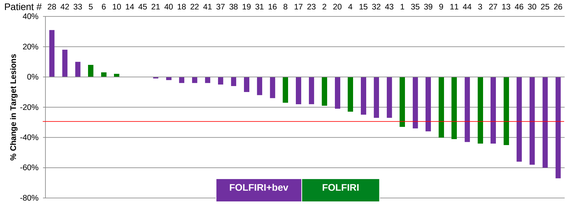
- **DCR (PR+SD) of 93%** (37 of 40 evaluable pts) with 13 pts with PR **(33%)** and 24 pts with SD.
- **DCR (PR+SD) of 90%** (18 of 20 evaluable pts previously exposed to FOLFIRI) with 6 pts with **PR (30%)** and 15 pts with tumor regression **(75%)**.
- **DCR (PR+SD) of 86%** (12 of 14 evaluable pts refractory to FOLFIRI) with 3 pts with **PR (25%)** and 9 pts with tumor regression **(64%)**.

Patient Summary

Patient ID	Chemotherapy Backbone	# of Prior Lines of Therapy	# of Prior Lines of Therapy: FOLFIRI	Refractory to FOLFIRI	Bevacizumab	Cetuximab	Panitumumab	Regorafenib	Weeks on Study	Best Response (RECIST v. 1.1)	Comment
1	FOLFIRI	4	Exposed	Yes	Exposed	Exposed	Exposed	Exposed	36	PR	33% tumor regression, prolonged SD
2	FOLFIRI	6	Exposed	No	Exposed	Exposed	Naive	Exposed	25	SD	19% tumor regression, prolonged SD
3	FOLFIRI	3	Exposed	No	Naive	Exposed	Naive	Naive	17	PR	44% tumor regression
4	FOLFIRI	3	Exposed	Yes	Exposed	Naive	Naive	Exposed	16	SD	23% tumor regression
5	FOLFIRI	2	Exposed	Yes	Exposed	Exposed	Naive	Naive	6	PD	8% tumor growth , unequivocal progression of non-target lesions
6	FOLFIRI	1	Naive	N/A	Naive	Naive	Naive	Naive	17	SD	6% tumor growth
7	FOLFIRI	1	Naive	N/A	Exposed	Naive	Naive	Naive	3	N/A	N/A
8	FOLFIRI	1	Naive	N/A	Naive	Naive	Naive	Naive	33	SD	17% tumor regression, prolonged SD
9	FOLFIRI	3	Exposed	No	Exposed	Naive	Naive	Naive	49	PR	40% tumor regression, prolonged SD / PR
10	FOLFIRI	4	Exposed	Yes	Exposed	Naive	Naive	Exposed	16	SD	2% tumor growth
11	FOLFIRI	1	Naive	N/A	Naive	Naive	Naive	Naive	37+	PR	41% tumor regression, prolonged SD / PR, continuing on study
12	FOLFIRI	1	Naive	N/A	Naive	Naive	Naive	Naive	4	N/A	N/A
13	FOLFIRI	1	Naive	N/A	Exposed	Naive	Naive	Naive	29+	PR	41% tumor regression, prolonged SD / PR continuing on study
14	FOLFIRI	2	Naive	N/A	Exposed	Naive	Naive	Naive	18	SD	0% tumor growth
15	FOLFIRI/Bev	1	Naive	N/A	Naive	Naive	Naive	Naive	105+	SD	25% tumor regression, prolonged SD, continuing on study
16	FOLFIRI/Bev	1	Naive	N/A	Naive	Naive	Naive	Naive	29	SD	14% tumor regression
17	FOLFIRI/Bev	9	Exposed	Yes	Exposed	Naive	Naive	Exposed	24	SD	18% tumor regression, prolonged SD
18	FOLFIRI/Bev	1	Naive	N/A	Exposed	Naive	Naive	Naive	18	SD	4% tumor regression
19	FOLFIRI/Bev	6	Exposed	No	Exposed	Exposed	Naive	Exposed	15	SD	10% tumor regression
20	FOLFIRI/Bev	7	Exposed	Yes	Exposed	Naive	Naive	Exposed	14	SD	21% tumor regression
21	FOLFIRI/Bev	3	Exposed	Yes	Exposed	Naive	Exposed	Naive	26	SD	1% tumor regression; prolonged SD
22	FOLFIRI/Bev	3	Exposed	No	Exposed	Naive	Naive	Naive	42	SD	4% tumor regression; prolonged SD
23	FOLFIRI/Bev	1	Naive	N/A	Naive	Naive	Naive	Naive	25	SD	18% tumor regression; prolonged SD
24	FOLFIRI/Bev	1	Naive	N/A	Exposed	Naive	Naive	Naive	5	N/A	N/A
25	FOLFIRI/Bev	3	Exposed	Yes	Naive	Naive	Naive	Naive	44	PR	45% tumor regression, prolonged SD / PR
26	FOLFIRI/Bev	0	Naive	N/A	Naive	Naive	Naive	Naive	58+	PR	67% tumor regression, prolonged PR, continuing on study
27	FOLFIRI/Bev	1	Naive	N/A	Naive	Naive	Naive	Naive	21	PR	44% tumor regression, prolonged PR
28	FOLFIRI/Bev	3	Exposed	Yes	Exposed	Naive	Naive	Exposed	10	PD	31% tumor growth
29	FOLFIRI/Bev	1	Naive	N/A	Naive	Naive	Naive	Naive	1	N/A	N/A
30	FOLFIRI/Bev	2	Exposed	No	Exposed	Naive	Naive	Naive	47	PR	58% tumor regression, prolonged PR
31	FOLFIRI/Bev	1	Naive	N/A	Exposed	Naive	Naive	Naive	45	SD	12% tumor regression, prolonged SD
32	FOLFIRI/Bev	2	Exposed	Yes	Naive	Naive	Naive	Naive	50	SD	27% tumor regression, prolonged SD
33	FOLFIRI/Bev	1	Naive	N/A	Exposed	Naive	Naive	Naive	41	SD	10% tumor growth, prolonged SD
34	FOLFIRI/Bev	1	Naive	N/A	Exposed	Naive	Naive	Naive	8	N/A	N/A
35	FOLFIRI/Bev	1	Naive	N/A	Exposed	Naive	Naive	Naive	26	PR	34% tumor regression, prolonged SD / PR
36	FOLFIRI/Bev	4	Exposed	Yes	Exposed	Naive	Naive	Naive	9	N/A	N/A
37	FOLFIRI/Bev	1	Naive	N/A	Exposed	Naive	Naive	Naive	34	SD	5% tumor regression, prolonged SD
38	FOLFIRI/Bev	1	Naive	N/A	Naive	Naive	Naive	Naive	18	SD	6% tumor regression
39	FOLFIRI/Bev	1	Naive	N/A	Exposed	Naive	Naive	Naive	20	PR	36% tumor regression
40	FOLFIRI/Bev	2	Exposed	Yes	Exposed	Naive	Naive	Naive	38+	SD	2% tumor regression, prolonged SD, continuing on study
41	FOLFIRI/Bev	1	Naive	N/A	Naive	Naive	Naive	Naive	9	PD	4% tumor regression, new lesions
42	FOLFIRI/Bev	1	Naive	N/A	Naive	Naive	Naive	Naive	16	SD	18% tumor growth
43	FOLFIRI/Bev	2	Naive	N/A	Naive	Exposed	Naive	Naive	17	SD	27% tumor regression, prolonged SD
44	FOLFIRI/Bev	0	Naive	N/A	Naive	Naive	Naive	Naive	32+	PR	43% tumor regression, prolonged PR, continuing on study
45	FOLFIRI/Bev	3	Exposed	Yes	Exposed	Naive	Naive	Naive	11	SD	0% tumor growth
46	FOLFIRI/Bev	3	Exposed	Yes	Exposed	Naive	Naive	Naive	27+	PR	56% tumor regression, prolonged PR, continuing on study

Prolonged response is defined as a response shown in two or more consecutive reassessment scans, separated by approximately 8 weeks.
FOLFIRI-refractory status is defined as progressive disease during or < 3 months after the last dose of FOLFIRI.
Data cut-off date: May 17th, 2016.

% Change in Target Lesions (Best Response)



CONCLUSIONS

- Napabucasin was safely combined with FOLFIRI with or without bev with no new adverse events observed and no evidence of pharmacokinetic interaction noted. Napabucasin 240 mg BID was determined to be the recommended dose for combination with FOLFIRI with or without bev in further clinical studies.
- Gastrointestinal AEs seen with napabucasin in combination with FOLFIRI with and without bev were reversible and manageable with symptom medications .
- Encouraging signs of anti-cancer activity were observed in pts with advanced CRC who had failed prior standard chemotherapies, including in pts refractory to FOLFIRI.
- These results warrant further development of napabucasin in combination with FOLFIRI with and without bev in advanced CRC.