BBI608-201: Phase Ib/II Study of Cancer Stemness Inhibitor BBI608 Combined with Paclitaxel in Advanced Gastric and Gastroesophageal Junction (GEJ) Adenocarcinoma

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ABSTRACT

Background:

BBI608, a first-in-class CSC inhibitor that works through inhibiting Stat3, has shown potent synergistic anti-tumor and anti-metastatic activity with paclitaxel *in vivo*. In a phase Ib dose escalation study in patients with advanced solid tumors, BBI608 plus weekly paclitaxel was well tolerated and a RP2D of BBI608 500 mg BID was determined.

Methods:

Patients with advanced, pre-treated gastric and GEJ adenocarcinoma were enrolled in a phase Ib/II extension study to assess safety, tolerability, and preliminary anti-cancer activity in patients with advanced gastric/GEJ adenocarcinoma. Eligible patients received ≥1 line of prior treatment in the metastatic setting with a platinum and a fluoropyrimidine/TS inhibitor. BBI608 was administered orally at 480 mg or 500 mg twice daily with paclitaxel 80 mg/m² IV weekly 3 of every 4 weeks. A sample size of 40 set the bounds of the 90% CI at ±10% to 14%, assuming a DCR of 60% to 80%.

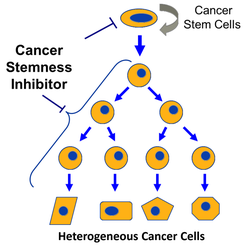
Results:

46 patients (87% Caucasian, 7% Black, 6% Asian) were enrolled in US and Canada; 10 (22%) had 1 line of prior therapy, 16 (35%) had 2 prior lines, and 20 (43%) had 3 or more prior lines. Common adverse events (AE) were grade 1 to 2 diarrhea, abdominal cramps, nausea, and vomiting. Grade 3 AE included vomiting (9%), diarrhea of 5 days or longer (7%), fatigue (7%), and abdominal cramps, nausea, dehydration (2% each). In 20 patients who had not received a taxane in the metastatic setting, the per-protocol ORR was 31% (5/16) and DCR was 75% (12/16); median PFS was 20.6 wks and mOS was 39.3 wks. In 26 patients who failed a prior taxane (median 3 prior lines), per-protocol ORR was 11% (2/19), and DCR was 68% (13/19); mPFS was 12.6 wks and mOS was 33.1 wks. In a subset of evaluated patients who received only 1 prior line of therapy without a taxane, the ORR was 50% (3/6) and the DCR was 83% (4/6).

Conclusions:

In this first known clinical study of a CSC inhibitor in gastric/GEJ adenocarcinoma, BBI608 and weekly paclitaxel were combined safely at the full-intended doses. Encouraging signs of anti-cancer activity were observed. A phase 3 study of BBI608 in combination with weekly paclitaxel in patients with gastric/GEJ cancer who had failed first line therapy is underway.

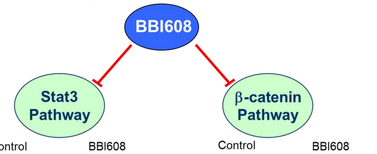
BACKGROUND

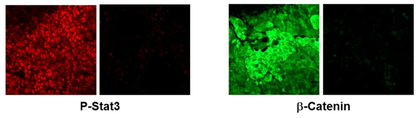


Cancer Stem Cells (CSC)

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

BBI608 is a *first-in-class* Cancer Stemness Inhibitor

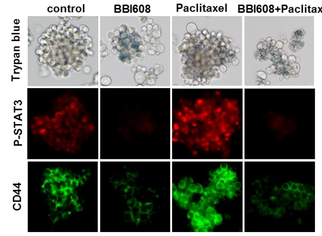




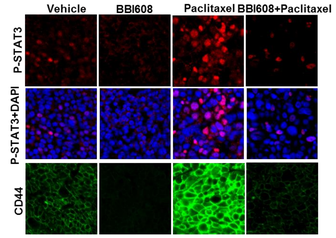
Effect of BBI608 Treatment on p-Stat3 and β-catenin Protein Levels in Human Colon Cancer Xenograft Tumor (SW480) in Nude Mice. Formaldehyde-fixed tumors from mice treated daily for 15 days with oral gavage of BBI608 or Vehicle (Control) were sectioned and analyzed by immunofluorescence staining using antibodies specific for human p-STAT3 and β-catenin.

COMBINATION RATIONALE

***In-Vitro* Cancer Stem Cell Spheres**



***In-Vivo* Biomarker Response in Xenograft Tumor**



TRIAL DESIGN

Phase Ib Objective:

- To determine the safety, tolerability and recommended Phase 2 dose (RP2D) of BBI608 given orally, twice daily, in combination with weekly paclitaxel (80 mg/m²)

Phase II Objective:

- To evaluate the preliminary anti-cancer activity of the combination regimen in selected diseases of interest

Key Design Elements:

- Open label phase Ib dose-escalation study followed by phase II expansion in several tumor types, including gastric/GEJ adenocarcinoma
- Patients with gastric or GEJ adenocarcinoma must have received previous treatment with a platinum/fluoropyrimidine doublet regimen in the metastatic setting
- Patients who received a platinum/fluoropyrimidine based regimen in the adjuvant setting could enroll if recurrence occurred within 6 months of regimen completion.
- Patients known to be positive for HER2 must have had prior treatment with trastuzumab
- BBI608 administered at 500 mg BID (using 125 mg capsules) or 480 mg BID (using 80 mg capsules)
- Paclitaxel (80 mg/m2) administered once weekly as IV infusion over one hour on 3 of every 4 weeks.
- Objective tumor response assessed every 8 weeks using Response Evaluation Criteria In Solid Tumors (RECIST 1.1).

PATIENT CHARACTERISTICS

- For most patients (78%), protocol therapy was the 3rd or later line of therapy received
- 26 out of 46 patients (57%) had previously received a taxane-based regimen in the metastatic setting

Study Population N = 46

Age		
Median	60	*yrs*
Range	36 - 84	*yrs*

Gender	N	%
Female	10	22%
Male	36	78%

Race	N	%
Caucasian	40	86%
Asian	3	7%
Black	3	7%

Ethnicity	N	%
Hispanic	2	4%
Non-Hispanic	44	96%

Karnofsky	N	%
100%	4	9%
90%	15	33%
80%	21	46%
70%	6	13%

Prior Regimen	N	%
1 prior	10	22%
2 prior	16	35%
≥3 prior	20	43%

Prior Taxane	N	%
No	19	41%
Yes	27	59%

Taxane Setting	N	%
Neoadjuvant	1	4%
Metastatic	26	96%

COMBINATION REGIMEN SAFETY PROFILE

- The combination of BBI608 and weekly paclitaxel was well tolerated in this cohort

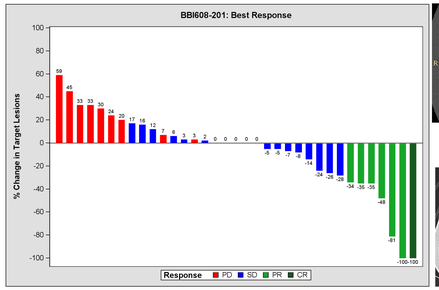
BBI608-201 Adverse Events N = 46

System	Event Term	Grade 1 #	Grade 1 %	Grade 2 #	Grade 2 %	Grade 3 #	Grade 3 %
Gastrointestinal	Diarrhea	35	76.1%	13	28.3%	3*	6.5%
	Nausea	19	41.3%	11	23.9%	1	2.2%
	Vomiting	11	23.9%	6	13.0%	4	8.7%
	Abdominal Pain	12	26.1%	7	15.2%	1	2.2%
	Bloating	2	4.3%	2	4.3%	0	0.0%
	Gastrointestinal Pain	1	2.2%	1	2.2%	1	2.2%
	Flatulence	1	2.2%	1	2.2%	0	0.0%
	Constipation	1	2.2%	0	0.0%	0	0.0%
	Dry Mouth	1	2.2%	0	0.0%	0	0.0%
	Reflux	1	2.2%	0	0.0%	0	0.0%
Constitutional	Fatigue	19	41.3%	13	28.3%	3	6.5%
	Weight Loss	1	2.2%	2	4.3%	0	0.0%
	Malaise	1	2.2%	1	2.2%	0	0.0%
	Neutrophil Count Decreased	0	0.0%	1	2.2%	0	0.0%
	White Blood Cell Decreased	0	0.0%	0	0.0%	1	2.2%
Metabolism And Nutrition	Anorexia	16	34.8%	8	17.4%	1	2.2%
	Dehydration	2	4.3%	5	10.9%	1	2.2%
Renal And Urinary	Urine Discoloration	5	10.9%	1	2.2%	0	0.0%
	Proteinuria	0	0.0%	1	2.2%	0	0.0%
	Acute Kidney Injury	0	0.0%	0	0.0%	1	2.2%
Skin & Subcutaneous Tissue	Alopecia	3	6.5%	0	0.0%	0	0.0%

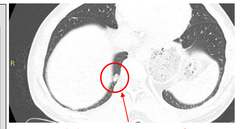
**symptom duration of 5 days or longer; 9 total had grade 3 diarrhea of any duration*

ANTI-CANCER ACTIVITY

- Early signs of anti-cancer activity in patients with gastric/GEJ adenocarcinoma were confirmed in an expansion cohort of heavily pre-treated gastric/GEJ patients

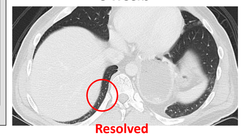


BASELINE



2.2 cm RLL metastasis

8 Weeks



Resolved

EFFICACY - SUMMARY

Group	N	Prior Lines (ave.)	ORR (%)	DCR (%)	mPFS (weeks)	mOS (weeks)
All Patients:	46	2.4	15%	54%	13.0	31.6
Total Evaluated Per-Protocol:	35	2.4	20%	71%	14.6	34.0
Received Taxane in Metastatic Setting:	19	2.6	11%	68%	12.6	33.1
No Taxane in Metastatic Setting:	16	2.1	31%	75%	20.6	39.3

- **In 6 patients evaluated who received 1 prior line of therapy that did not include a taxane, an objective response rate of 50% was observed.**
- BBI608 plus weekly paclitaxel for the treatment of patients with gastric/GEJ adenocarcinoma who have failed first line platinum-based therapy is being evaluated in a phase III randomized controlled trial, the BRIGHTER trial *(Abstract: Trials in Progress 4139, Board #: 247a)*.

CONCLUSIONS

- BBI608 at doses of 480 mg BID and 500 mg BID plus weekly paclitaxel (80 mg/m²) is well tolerated in patients with advanced gastric/GEJ adenocarcinoma
- Lesion regression, objective responses, and prolonged stable disease was observed in heavily pre-treated patients
- In 20 previously treated patients who had not received a taxane in the metastatic setting (average of 2 prior lines), an objective response rate of 25% was observed in the intention to treat population (31% in the per-protocol population)
- Evaluated patients who received 1 prior line of therapy had an objective response rate of 50%. The BRIGHTER Trial will further investigate this promising sub-population *(Abstract: Trials in Progress 4139, Board #: 247a)*