ABSTRACT

Background: BBI608 is a first-in-class cancer stemness inhibitor that blocks βcatenin-mediated transcription of cancer stemness genes. Preclinical and GDC activity was observed in vitro and in vivo, in mouse and combination therapies. In the trial, BBI608 was generally well-tolerated with encouraging signs of anti-tumor activity.

Methods: A phase Ib open label, multi-center study in patients (pts) with advanced CRC included 3 arms: Napabucasin (Nab) alone, Napabucasin/Bev (Nab+Bev) without BBI608, or Napabucasin/Bev in combination with BBI608. Patients were enrolled in 3 cohorts of 6 pts. co-treated with BBI608 at 240 mg BD in combination with fluorouracil (FU) (400 mg/m² w/bd) with 2400 mg/m²,330 mg/m² and 850 mg/m². Napabucasin 850 mg/m² was co-administered with or without bevacizumab 5 mg/kg, administered beginning 1 week after bevacizumab, until disease progression, unacceptable toxicity, or other discontinuation criteria was met.

Results: 18 heavily pretreated pts, with an average of >18 prior lines of therapy, of which 8 pts (44%) previously progressed on FOLFIRI, were enrolled. 6 of 18 pts received both Napabucasin and bevacizumab in combination with BBI608. Most common adverse events (AE) grade 1 and 2 adverse events were fatigue, rash, nausea, diaphoresis, and constipation. No unexpected events and/or an increased frequency as compared to single agents profile was similar to that of each regimen as monotherapy. Grade 1 events related to protocol therapy included decreased appetite in 4%, fatigue in 2%, myalgia in 1% and hearing loss in 1% in all events observed after dose reduction and/or start of anti-diarrheal medications. No significant pharmacokinetic interactions were observed. Disease control rate (DCR) was observed in 24 of 27 evaluable pts (92%) with 1 PR (RECIST 1.1), 6 pts (22%) and/or SD (19%) which included 2 narcotic Arms (majority of tumor regression, 14% tumor regression, prolonged stable disease, 25% tumor regression, prolonged stable disease), 19% tumor regression, prolonged stable disease. 77.8% of pts were still on study and 100% had achieved disease control (PR or SD) after 24 weeks.

Conclusions: This phase I/II study confirmed that BBI608 at 240 mg BD can be safely combined with FOLFIRI with or without bevacizumab, and shows encouraging anti-tumor activity in heavily pretreated CRC pts, even in pts with prior progression on FOLFIRI based therapy.

BACKGROUND

Cancer Stem Cells (CSC) and Cancer Stemness
- Highly Tumorigenic
- Evolutionarily responsible for continuous malignant growth
- Evolution (allo)plasticity
- Resistance to chemotherapy and current targeted therapies

BBI608 is a first-in-Class Cancer Stemness Inhibitor

COMBINATION RATIONALE
- The combination of BBI608 with 5-FU and irinotecan showed strong synergy in vitro and in vivo.

Effect of Treatment on Cancer Stem Cells

Patient Population

- Histologically confirmed advanced CRC that is metastatic, unresectable, or recurrent and for which FOLFIRI is or without bevacizumab is an acceptable therapeutic option.
- Pretreated with standard chemotherapy.
- Karnofsky performance status of ≥70%.

Combination Regimen Safety Profile

- 18% tumor regression, prolonged stable disease, 25% tumor regression, prolonged stable disease.
- 19% tumor regression, prolonged stable disease.
- 77.8% of pts were still on study and 100% had achieved disease control (PR or SD) after 24 weeks.

Conclusions

- BBI608 can be safely combined with FOLFIRI with or without bevacizumab with no new adverse events and in absence of pharmacokinetic interaction.

Study Design

- Open label, multi-center, phase II study.
- Combination and/or standard FOLFIRI with or without bevacizumab every 14 days.
- Pharmacokinetics and pharmacodynamics were evaluated.
- Objective tumor response assessed every 8 weeks using Response Evaluation Criteria in Solid Tumors (RECIST 1.1).

% Change in Target Lesions (Best Response)

- 18% tumor regression, prolonged stable disease, 25% tumor regression, prolonged stable disease.
- 19% tumor regression, prolonged stable disease.
- 77.8% of pts were still on study and 100% had achieved disease control (PR or SD) after 24 weeks.

Conclusions

- BBI608 can be safely combined with FOLFIRI with or without bevacizumab with no new adverse events and in absence of pharmacokinetic interaction.

Hematologic & Non-Hematologic Adverse Events by Grade

- No evidence of significant pharmacokinetic interactions.

- BBI608 can be safely combined with FOLFIRI with or without bevacizumab with no new adverse events and in absence of pharmacokinetic interaction.

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