Targeting Innate Immunity with BXCL701 in Combination with Pembrolizumab in Patients with Advanced Solid Cancers: Phase 2 Basket Study

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BACKGROUND

- BXCL701 is a first-in-class oral small molecule competitive inhibitor of dipeptidyl peptidases (DPP) DPP8 and DPP9
- BXCL701 activates inflammasome mediated pyroptosis to alert and prime adaptive immune cells, leading to induction of IL-18 and IL-1ß, bridging between innate and adaptive immunity.
- BXCL701 mediated activation of innate immunity has been shown to complement T-cells targeting immunotherapy in syngeneic animal models, significant tumor responses were observed with BXCL701 plus checkpoint inhibition

Figure 1: BXCL701 mechanism of action

Figure 2: Macrophage pyroptosis is the central component of BXCL701 activity through DPP8/9 inhibition.

- Inhibition of DPP8/9 has been shown to activate the pro-inflammatory process of pyroptosis in macrophages.
- Macrophage pyroptosis through the Nlrp1b pathway has been shown to drive the activation of caspase-1 and subsequent activation of pro-IL-18 and pro-IL-1β leading to the production of a host of cytokines and chemokines including IL-18 and IL-1β
- Mouse genetics further supports this process as the driver of BXCL701 activity via inhibition of DPP8/9

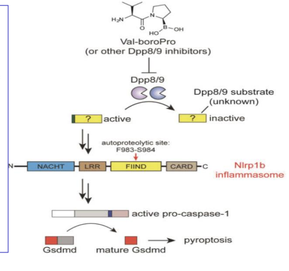
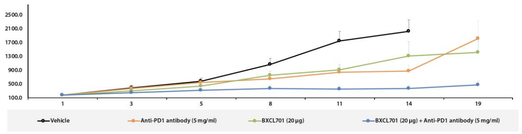


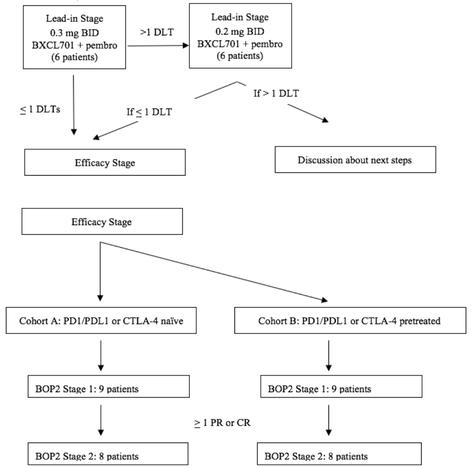
Figure 3: BXCL701 and PD-1 antibody in MC38 colon cancer model. BCL701 and PD1 antibody demonstrated

- Synergistic antitumor activity in MC38 colon cancer model.
- Synergistic upregulation in the immunomodulatory parameters for proinflammatory cytokines (IL-2, IL-12p40, IL-6), chemokines (GM-CSF), and memory T cells (IL-15, IL-7).
- Synergistic increase in the cytotoxic NK cells and macrophages in the tumor with a decrease in the immunosuppressive T-regs.



METHODS

Figure 4: Study scheme (9-34 patients)



Trial Design and Objectives

- Investigator-initiated study to evaluate dose limiting toxicities (DLT) of intravenous pembrolizumab 200 mg given every 3 weeks and oral BXCL701 0.3 mg BID given on Day 1-14 in the first 6 patients enrolled and to evaluate response rate per RECIST and iRECIST in patients, who are naïve to prior PD-1/PD-L1 or CTLA-4 inhibitors (Cohort A) or previously treated with PD-1/PD-L1 or CTLA-4 inhibitors (Cohort B).
- To evaluate progression-free survival (PFS), overall survival (OS), duration of response, and overall safety and tolerability .
- To evaluate the quantitative and qualitative effects of BXCL701 in combination with pembrolizumab on relevant immune effector cells and cytokines in tumor tissues and blood, respectively.
- To explore the predictive value of baseline PD-L1 tumor expression and tumor mutation burden (TMB) with clinical outcomes.
- To evaluate changes in serially collected blood circulating tumor DNA (ctDNA) to assess for tumor response and clonal evolution.

Major eligibility criteria

- Patients 12 years or older with advanced solid tumor malignancy
- Measurable disease per RECIST.
- ECOG 0-2
- ANC ≥ 1,000/uL
- Hemoglobin ≥ 8 g/dL
- Platelets ≥ 75,000/uL
- Total bilirubin ≤ 1.5 x upper limit of normal (ULN)
- ALT/AST ≤ 3 x ULN (5 x ULN for patients with liver metastasis)

RESULTS

Table 1: Patients characteristics (N=14 enrolled to date)

Characteristic	No. of patients (%)
Age, years	
Median (range)	63 (36-86)
Gender	
Male	9 (64)
Female	5 (36)
Cohort A (PD-1/PD-L1 or CTLA-4 naïve)	4
Cohort B (PD-1/PD-L1 or CTLA-4 pretreated)	10
Tumor type	
Castrate resistant prostate cancer	2
Colon cancer	1
Endometrial cancer	1
Dedifferentiated liposarcoma	1
Basal cell carcinoma	1
Squamous cell carcinoma of unknown primary	1
Uveal melanoma	1
Leiomyosarcoma	1
Skin melanoma	1
Uterine sarcoma	1
TNBC	1
Pleomorphic sarcoma	1
Astrocytoma	1

Safety

Safety summary for Lead-in stage

- Grade 4 hypotension with syncope on Day 6 of Cycle 1 related to BXCL701in a patient with endometrial cancer was the only DLT. The patient fully recovered with appropriate medical care.

Safety summary for Efficacy stage

- Grade 4 hypotension related to BXCL701 with subsequent cardiac arrest and death on Day 5 of Cycle 1.
- Other adverse events present in more than 5% of patients included manageable grade 1 or 2 edema, flu-like symptoms, fever, fatigue, nausea, vomiting and maculopapular rash rash
- Because of two episodes of grade 4 hypotension the enrollment is currently on hold while the protocol is being amended to include risk mitigation strategies.

Efficacy

Summary for Cohort A: PD-1/PD-L1 and/or CTLA-4 naïve (N=4)

- 1 **PR** (-64%) in a patient with MSS endometrial carcinoma, PD-L1 negative (CPS <1)
- 1 SD (-7%) in a patient with basal cell carcinoma, PD-L1 negative

Summary for Cohort B: PD-1/PD-L1 and/or CTLA-4 pretreated (N=9)

- 1 **PR** (-31%) in a patient with uveal melanoma , PD-L1 negative
- 1 SD (-23%) in a patient with high grade pleomorphic sarcoma, MSS, PD-L1 negative
- Additional SDs were observed in a patient with squamous cell carcinoma of unknown primary (+4%) and uterine sarcoma (+5%)

RESULTS

Figure 5: Best change in sum of target lesions per RECIST 1.1

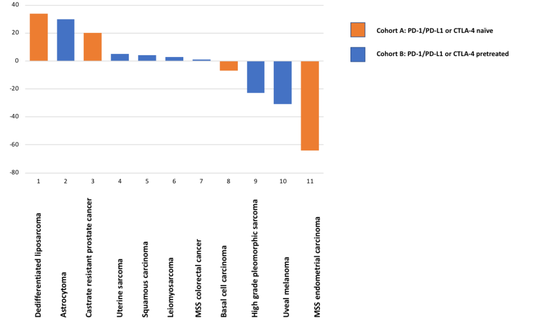
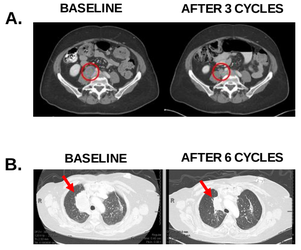


Figure 6:

Partial response (-64%) in a patient with MSS, PD-L1 negative endometrial cancer and 2 prior systemic therapies not including PD-1/PD-L1 or CTLA-4 inhibitors. The patient continues on study for more than 4 months (**A.**).

Stable disease (-23%) in a patient with high grade pleomorphic sarcoma, MSS, PD-L1 negative and 3 prior systemic therapies including PD1 antibody (best response: PD). The patient continues on study for more than 5 months (**B.**).



CONCLUSIONS

- BXCL701 in combination with pembrolizumab demonstrated encouraging activity in patients with and without prior treatment with PD-1/PD-L1 and/or CTLA-4 inhibitors.
- Two episodes of grade 4 hypotension during the first week of therapy resulted in protocol amendment to include risk mitigation strategies (e.g. intra-patient dose-escalating dosing schedule, ambulatory blood pressure monitoring).
- Encouraging activity justifies both cohorts to advance to 2nd stage of enrollment once the risk mitigation strategies for hypotension are implemented.

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