BXCL701, first-in-class oral activator of systemic innate immunity pathway combined with pembrolizumab (Keytruda), in men with metastatic castration-resistant prostate cancer (mCRPC)

Abstract #124

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BACKGROUND

METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (mCRPC) - UNMET MEDICAL NEED

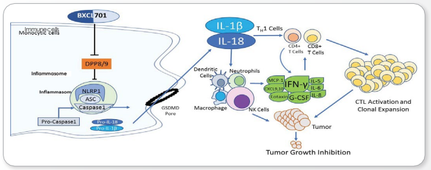
- American Cancer Society estimates ~191,930 new cases of prostate cancer in U.S. for 2020, 10–20% develop CRPC within approximately 5 years of follow up, most of them having metastases at time of diagnosis
- Treatment of mCRPC has evolved rapidly over the past few years: first line treatment with androgen deprivation therapy (ADT) or one of the newer androgen signaling inhibitors (ASI), abiraterone or enzalutamide followed by chemotherapy with docetaxel is now standard of care. Docetaxel is associated with a median overall survival of less than 2 years
- Despite demonstrated benefit of immunotherapies targeting PD-1—such as pembrolizumab—on clinical outcomes in many solid tumors, mCRPC remains largely resistant to such therapies with single agent response rates around 6% (Keynote 199 ASCO-GU 2020). Further exploration has been focused on combination therapies.
- The BXCL701 immunomodulatory mechanism may manipulate the tumor micro-environment in such a way to convert a "cold" tumor environment into an inflamed "hot" environment so that prostate cancer can overcome resistance to immunotherapy

BXCL701 MECHANISM OF ACTION

- A critical role of the innate immune system is to alert the adaptive immune system of an invading pathogen
  - Induction of Inflammation mediated through cytokines – Stimulation of antigen presentation by professional antigen presenting cells
- BXCL701 (Talabostat/Val-boroPro) is a potential first-in-class oral small molecule inhibitor of dipeptidyl peptidases (DPP) DPP8 and DPP9

- BXCL701 is designed to trigger the inflammasome to alert and prime immune cells, leading to induction of IL-18 and IL-18, bridging between innate and adaptive immunity
- Activation of innate immunity by BXCL701 has been shown to complement T-cells targeting immunotherapy: in syngeneic animal models, significant tumor responses were observed with a combination of BXCL701 and checkpoint inhibition

BXCL701 ACTIVTY IS MEDIATED BY DPP8/9 INHIBITION

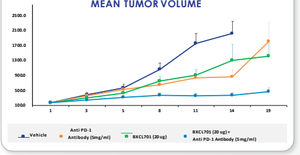


- Inhibition of DPP8/9 has been shown to activate the inflammasome, and thus the pro-inflammatory process in monocytic and other immune cells.
- The Nlrp1b inflammasome pathway drives the activation of caspase-1 and the eventual production of a host of cytokines and chemokines including IL-18 and IL-1β.
- The Cytokine/Chemokine signaling leads to increase in immune cell infiltration, cells monocytes, NK cells and T lymphocytes which inhibit tumor growth and induce tumor cell killing.
- The cytokine and chemokine release may also facilitate increased tumor cell sensitivity and synergistic anti-tumor activity when combined with other agents that target the adaptive immune response such as checkpoint inhibitors which target T-cells.

Okondo MC et al. Cell Chem Biol.2018

PRECLINICAL DATA VALIDATES BXCL701 AND ANTI-PD1 COMBINATION POTENTIAL

TREATMENT EFFECT OF BXCL701 WITH ANTI-PD-1 ON MEAN TUMOR VOLUME



BXCL701/ANTI-PD-1 COMBINATION SHOWED

- Synergistic antitumor effect on tumor volume in MC38 mouse model of colon adenocarcinoma
- Synergistic upregulation in the immunomodulatory parameters for pro-inflammatory cytokines*, chemokines+ and associated memory T-cells# by dose as single agent and in combination
- Synergistic increase in the cytotoxic NK cells and macrophages in the tumor with a decrease in the immunosuppressive T-regs

*IL-2, IL-12p40, IL-6; +GM-CSF, G-CSF; #IL-15, IL-7

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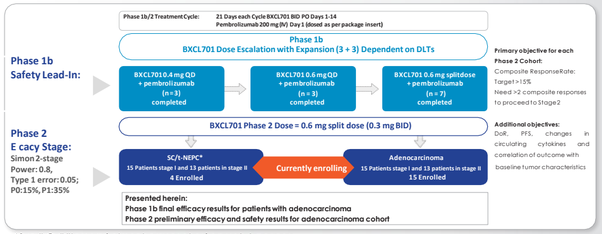
METHODS

TRIAL SCHEMATIC AND KEY OBJECTIVES



*Small-Cell/therapy-induced neuroendocrine prostate cancer

KEY INCLUSION AND EXCLUSION CRITERIA

KEY INCLUSION CRITERIA

- Progression as defined by PCWG3 criteria
- At least 1 prior line of systemic therapy for locally advanced or metastatic prostate cancer
- Serum testosterone <50 ng/dL during screening except for those with de novo small cell prostate cancer
- Eastern Cooperative Oncology Performance status of 0-2 Group (ECOG)
- Phase 2 Efficacy Stage only:
  - For Cohort A (SCNC):
    - At least 1 prior line of chemotherapy
    - Measurable disease by RECIST 1.1
  - For Cohort B (Adenocarcinoma):
    - At least 1 but no more than 2, androgen signaling inhibitors (ASI) and at least 1 prior line of taxane containing chemotherapy
    - Measurable disease by RECIST 1.1 or bone mets

KEY EXCLUSION CRITERIA

- More than 2 cytotoxic chemotherapy regimens for mCRPC
- Prior treatment with an anti-PD-1, anti-PD-L1, anti-programmed death-ligand 2 (PD-L2) agent or with an agent directed to another co-inhibitory T-cell receptor
- Additional active malignancy that may confound the assessment of the study endpoints
- Brain metastases that are symptomatic and progressive on imaging
- Significant cardiovascular or pulmonary disease
- History of symptomatic orthostatic hypotension with 3 months prior to enrollment

See ClinicalTrials.gov Identifier: NCT03910660 for more details

PHASE 1B RESULTS SUPPORT BID DOSING OF BXCL701 + PEMBROLIZUMAB

- On-target adverse events consistent with cytokine activation were seen at the highest daily dose tested (0.6 mg total daily dose)
  - Splitting the daily dose was associated with improved tolerability as evidenced by no reported DLTs and lower rates of other adverse events of interest such as hypotension and peripheral edema
- Consistent dose and time dependent increases in IL-18 and IFN-γ levels observed in 0.6 mg split dose, maximal changes noted after 14 days of continuous dosing. Minimal and short-duration changes noted in cytokines often associated with AEs

Presented at SITC 2020 Poster 341

PHASE 1B KEY SAFETY SUMMARY

	BXCL701 0.4 mg qd + pembrolizumab n = 3				BXCL701 0.6 mg qd + pembrolizumab n = 3				BXCL701 0.6 mg Split dose + pembrolizumab n = 7			
	(Grade) n											
BXCL701 Related Events#	(Any)	(1)	(2)	(3)	(Any)	(1)	(2)	(3)	(Any)	(1)	(2)	(3)
Hypotension*	-	-	-	-	3	2	1	-	1	1	-	-
Dizziness	-	-	-	-	2	2	-	-	-	-	-	-
Headache	-	-	-	-	1	1	-	-	-	-	-	-
Syncope	-	-	-	-	1	-	-	1	-	-	-	-
Dyspnea	-	-	-	-	1	1	-	-	1	-	1	-
Chills	-	-	-	-	-	-	-	-	1	-	1	-
Edema	-	-	-	-	2	1	1	-	-	-	-	-
Fatigue	-	-	-	-	1	-	1	-	3	2	-	1†
Myalgia	-	-	-	-	1	1	-	-	1	1	-	-

*# Relatedness as assessed by investigator, *Includes orthostatic hypotension, † Fatigue present at baseline*

Other BXCL701 Related Adverse Events Grade ≥3 (1 acidosis) or Low Grade in ≥2 patients (arthralgia, hematologic, decrease appetite)

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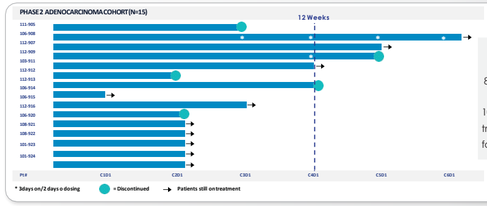
RESULTS

PRELIMINARY RESULTS AS OF 1/12/21 UNLESS NOTED OTHERWISE

Baseline Characteristics		Phase 2 Adenocarcinoma Cohort n (%)
Enrolled		15
Age (years) (n=12)	Mean (range)	70 (58-80)
ECOG Performance Status	0 1 Not available	7 (47%) 7 (47%) 1 (6%)
Prior Systemic Therapies (n=13)	1st Generation androgen deprivation therapy 2nd Generation androgen signaling inhibitor Chemotherapy Other Systemic Therapies PSMA based therapy Sipuleucel-T	6 (46%) 12 (92%) 13 (100%) 1 (8%) 5 (38%)

EXPOSURE DURATION AND SUBJECT DISPOSITION



Median duration on-treatment:

8+ weeks (2.7+ cycles), range 1-18+ weeks

10 patients remain on treatment including 3 for more than 12 weeks

* 3days on/2 days off dosing Discontinuations for reasons other than disease progression:
Patient 112-909 Withdrew consent refused further treatment | Patient 112-912 Withdrew consent refused further treatment
Patient 112-916 Investigator Decision

PRELIMINARY ACTIVITY OBSERVED IN ADENOCARCINOMA POPULATION

Best Response	Phase 1b Population Total = 7 n (%)	Phase 2 Population Total = 15 n (%)
RECIST 1.1 by Investigator Assessment+		
Evaluable	7	5
Measurable	4 (57%)	4 (80%)
Best RECIST Response		
PR	1 (14%)	0
SD (time duration) Including Minor Response	3 (43%)	3 (60%) 2 (40%)
Disease Control Rate (PR + SD + Non-CR/Non-PD)	7 (100%)	4 (80%)
PD	0	1 (20%)
PSA		
PSA Evaluable§	7	10
PSA50 Response	1 (14%)	1 (10%)
CTC		
CTC Evaluable¢	3	4
CTC Response#	0	1 (25%)
Composite Response	1 of 7 evaluable	1 of 10 evaluable todate

+Patients who received ≥1 dose of study therapy and 1 on-treatment tumor assessment

§Baseline value >4ng/mL and one on-treatment PSA assessment

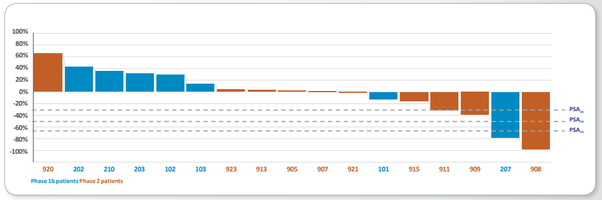
¢Baseline CTC value ≥5/7.5mL and one measurable on-treatment assessment

#CTC conversion from ≥5/7.5mL to <5/7.5mL

CTC data cut-off 1/04/21

SERUM PSA BEST OVERALL CHANGE

6/17 (35%) HAD ANY PSA REDUCTION, 2/17 HAD A PSA70 RESPONSE



RESPONDING PATIENT PROFILES

PID 207: RECIST 1.1 and PSA Response

- Prior systemic therapy included bicalutamide, abiraterone + prednisone, enzalutamide, sipuleucel, docetaxel + cabazitaxel
- Tempus molecular testing cfDNA peripheral blood: MSI-high not detected; no reportable treatment options found
- Duration of BXCL701 + pembrolizumab: 16+ cycles
- PSA50 response by 6 weeks, max reduction 84%. Baseline PSA 163.1 ng/mL
- RECIST 1.1 partial response by 12 weeks 35% reduction in target lesions (lymph), disappearance of 2/5 non-target lymph

PID 908: PSA/CTC Response with Minor Response in Target Lesions

- Prior systemic therapy included leuprolide, sipuleucel, enzalutamide, docetaxel, cabazitaxel
- Duration of BXCL701 + pembrolizumab: 5+ cycles
- PSA50 response at 3 weeks, ongoing at 15 weeks (from 25 ng/mL to 0.2 ng/mL – 99% reduction)
- CTC conversion at 3 weeks
- RECIST 1.1 minor response (on-going) - 19% reduction in target lesions (liver, lymph)

PID 909: Minor Response in Target Lesions

- Prior systemic therapy included bicalutamide, leuprolide, enzalutamide, docetaxel, abiraterone + prednisone
- Duration of BXCL701 + pembrolizumab: 4 cycles
- PSA decline at 12 weeks (40% reduction from 111.4 ng/mL to 66.9 ng/mL)
- RECIST 1.1 Minor Response (on-going) 27% reduction in target lesions (lymph)

PHASE 2 SAFETY IN ADENOCARCINOMA POPULATION

Preferred Term	Grade n = 13			
BXCL701 Related Events#	Grade 1 n	Grade 2 n	Grade 3 n	Total n
Subjects with any event	12	7	4	13
Hypotension*	2	2	1	5
Fatigue	4	1	-	5
Nausea	4	1	-	5
Dizziness	1	2	1	4
Vomiting	4	-	-	4
Rash	3	-	-	3
Decreased appetite	3	-	-	3
Decreased platelet count	3	-	-	3
Blood lactic acid increased	-	-	2	2
Myalgia	1	-	1	2
Chills	2	-	-	2
Fever	2	-	-	2
Constipation	2	-	-	2
Dry mouth	2	-	-	2

- Majority of events were low grade.
- AEs consistent with cytokine activation were observed
- Grade 3 hypotension was observed during the first week of treatment in a patient who initiated dosing with 0.3 mg BID
  - Step-up dosing was then implemented for all new patients with BXCL701 0.2 mg BID day 1 through day 7. Escalation to 0.3 mg BID was permitted if no treatment related AEs Grade >1 or skipped doses due to hypotension or orthostasis occurred during the first week of treatment

Other BXCL701 Related Adverse Events were limited to Grade 1 hypoalbuminemia, AST increased, LDH increased, and hyponatremia in 2 patients each

Relatedness as assessed by investigator, *includes orthostatic hypotension

CONCLUSION

- Orally administered BXCL701 in combination with pembrolizumab demonstrated encouraging anti-tumor activity in heavily pre-treated, refractory mCRPC with adenocarcinoma phenotype, a setting where checkpoint inhibitor monotherapies have demonstrated limited clinical benefit and patients have limited treatment options
  - Despite limited efficacy follow-up in the Phase 2 portion of the study at this data cut-off, 1 ongoing patient has achieved a PSA70 response plus CTC response and has had a 19% decrease in target lesions. A second patient has had a 40% reduction in PSA with a 27% reduction in target lesions. The disease control rate, defined as PR + SD + non-CR/non-PD, is 80% among RECIST evaluable patients
  - In the Phase 1b, 1 ongoing patient with adenocarcinoma has a PSA70 response and a RECIST 1.1 partial response
  - Efforts are underway to identify a potential predictive biomarker
- The BID dosing schedule for BXCL701 continues to demonstrate an acceptable safety profile when given in combination with pembrolizumab with primarily low grade on-target adverse events consistent with cytokine activation
- This study continues to enroll patients with adenocarcinoma and SC/t-NEPC as per protocol

THANK YOU

BioXcel Therapeutics would like to thank all patients, their families, and caregivers who made this study possible. BioXcel would also like to thank the participating investigators and their staff for their support on this study and their dedication to their patients, despite the additional challenges as a circumstance of the COVID-19 pandemic.