BXCL701—1st-in-class oral activator of systemic innate immunity—combined with pembrolizumab, in patients with metastatic castration-resistant prostate cancer (mCRPC) of adenocarcinoma phenotype: Phase 2a results

E-POSTER 125

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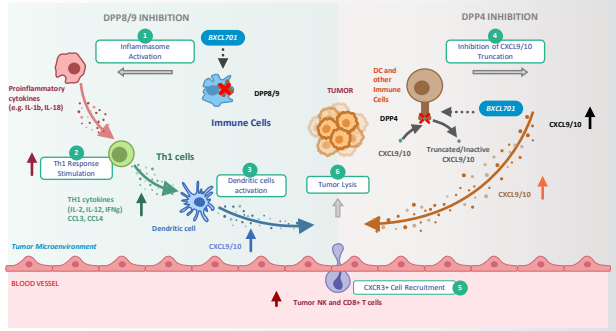
BACKGROUND

Metastatic Castration-Resistant Prostate Carcinoma (mCRPC)

- Approximately 268,490 new cases of prostate cancer in US in 2022[1]
- 10–20% develop CRPC within ~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:
  - 1st-line treatment with androgen deprivation therapy or one of newer androgen signaling inhibitors (ASI) abiraterone or enzalutamide followed by chemotherapy with docetaxel now standard of care
  - Docetaxel associated with median overall survival <2 years
- mCRPC remains largely resistant to PD-1 inhibitors, e.g., pembrolizumab[2]
  - Single agent objective response rate 3%-5%
  - Disease control rate 12%
  - PSA_{50} response 6%
- Further exploration has been focused on combination therapies
- BXCL701 immunomodulatory mechanism may turn a "cold" tumor micro-environment into an inflamed "hot" tumor micro-environment, contributing to overcome resistance to immunotherapy

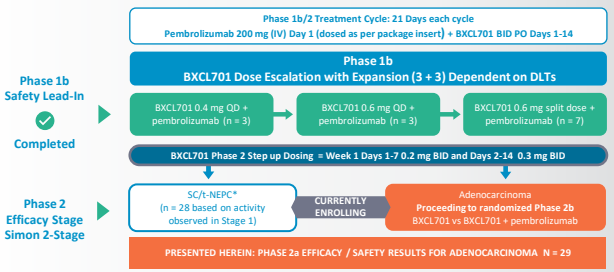
[1] The American Cancer Society's estimates for prostate cancer in the United States for 2022 [2] KEYNOTE-199—Journal of Clinical Oncology 38, no. 5 (February 10, 2020) 395-405. DOI: 10.1200/JCO.19.01638

BXCL701 MODULATES TUMOR MICROENVIRONMENT BY ACTIVATING INNATE IMMUNITY FOLLOWED BY ADAPTIVE IMMUNITY, LEADING TO CANCER CELL DEATH



Adapted from *Journal for ImmunoTherapy of Cancer 2021; 9:e002837*. doi:10.1136/jitc-2021-002837

METHODS | TRIAL SCHEMATIC AND KEY OBJECTIVES



Primary objective for each Phase 2 Cohort: Composite Response Rate, either objective response by RECIST 1.1 criteria, CTC Conversion from ≥5/7.5 mL to <5/7.5 mL, or ≥-50% PSA decline from baseline
Additional objectives: DoR, PFS, changes in circulating cytokines and correlation of outcome with baseline tumor characteristics
*Small-cell/treatment-emergent small-cell neuroendocrine prostate cancer

KEY INCLUSION AND EXCLUSION CRITERIA

KEY INCLUSION CRITERIA

- Histologically confirmed **adenocarcinoma**
- 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
- ECOG performance status of 0-2
- Phase 2 Efficacy Stage only:
  - **For Adenocarcinoma Cohort:**
    - 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 metastases

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
- History of symptomatic orthostatic hypotension within 3 months prior to enrollment

See ClinicalTrials.gov Identifier: NCT03910660 for more details

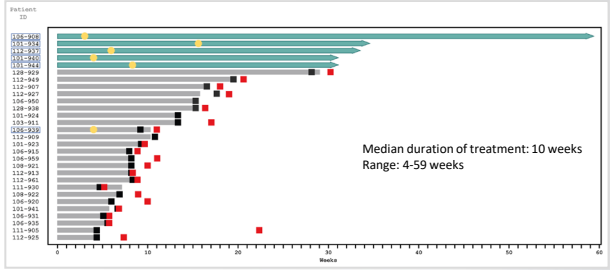
RESULTS: STUDY POPULATION

Patients Baseline Characteristics		Adenocarcinoma Cohort | n (%)
Enrolled Patients		**42**
Age (years)	**Mean** (SD) **Median** (Range)	**69.4** (8.76) **69.5** (51-87)
ECOG Performance Status	0 1 2	13 (31) 25 (60) 3 (7)
Bone Only disease		17 (40)
Prior Cancer Therapies	Mean number of prior regimens (SD)	5.3 (2.29)
Evaluable Patients		**29**
Prior Systemic Therapies	Previous targeted endocrine therapy *Enzalutamide only* *Abiraterone only* *Enzalutamide and abiraterone* Taxane Chemotherapy Provenge (sipuleucel-T) Radiation Therapy	 *5 (17)* *6 (21)* *17 (59)* 29 (100) 7 (24) 12 (41)

Data as of 24-NOV-2021 unless noted otherwise

EXPOSURE DURATION AND SUBJECT DISPOSITION

29 evaluable patients



EFFICACY RESULTS

Best Response	Phase 2a Adenocarcinoma Patients N = 29 (%) [95% Exact CI]
Composite Response	**6 (21) [8.0 – 39.7]**
Best RECIST 1.1 Response by Investigator Assessment	
RECIST Evaluable[a]	18 (62)
Partial Response	**4 (22) [6.4 – 47.6]**
Confirmed PR	*3 (75)*
Unconfirmed PR	*1 (25)*
SD (any duration) including Minor Response	11 (61)
Non-CR / Non-PD	15 (83)
PD	3 (17)
Disease Control Rate (CR + PR + SD)	**83%**
PSA	
PSA Evaluable[b]	29 (100)
PSA_{50} Response	**5 (17) [5.8 – 35.8]**
CTC[c]	
CTC Evaluable[d]	11 (38)
CTC Response[e]	**2 (18)**

Composite response rate: **21%**

- RECIST-defined PR*: **22%**
- Disease control rate: **83%**
- PSA_{50}: **17%**—including 5 patients with -100% to -57% PSA decrease
- CTC response: **18%**

** Includes confirmed and unconfirmed PRs*

Data cut-off date: 24-NOV-21

[a] Patients who received ≥2 cycles of study therapy and had 1 on-treatment tumor assessment [b] Baseline PSA >4 ng/mL and 1 on-treatment PSA assessment [c] Circulating tumor cell [d] Baseline CTC value ≥5/7.5 mL and 1 measurable on-treatment assessment [e] CTC conversion from ≥5/7.5 mL to <5/7.5 mL

EFFICACY SUMMARY

Data as of 24-NOV-2021

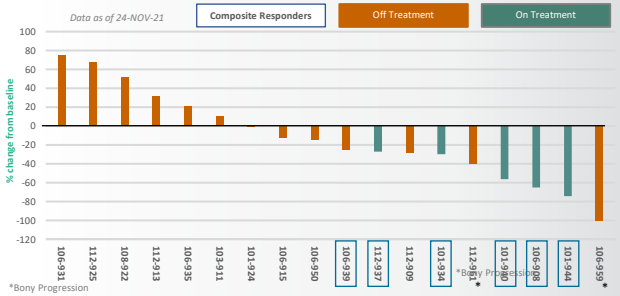
Patient	Prior Systemic Therapies	RECIST 1.1 ≥-30%*	CTC ≥5/7.5 ml to <5/7.5 ml*	PSA ≥-50%*	Tumor Biology
106-908	Enzalutamide, sipuleucel-T docetaxel, cabazitaxel	-65% Confirmed 59-week duration	5 to 0	-99%	TMB = 20.7 MSI High PD-L1 low
101-934	Nilutamide, abiraterone, enzalutamide sipuleucel-T docetaxel, cabazitaxel	-30% Unconfirmed 19-week duration	Baseline CTC = 0	-52%	TMB = 2 MSS PD-L1 low
112-937	Abiraterone, sipuleucel-T docetaxel	-27% 33-week duration		-98.5%	TMB = 1 MSS
106-939	Abiraterone, enzalutamide docetaxel, cabazitaxel	-24% 12-week duration	26 to 1	-57%	TMB = 4 MSS
101-940	Abiraterone, enzalutamide docetaxel, cabazitaxel	-56% Confirmed 31-week duration		-99.9%	MSS
101-944	Carboplatin docetaxel, cabazitaxel	-74% Confirmed 25-week duration	3 to 2	0%	TMB = 3 MSS PD-L1 low

On Treatment | Off Treatment | Response

Median duration of response: 28 weeks

**change from baseline | TMB = Tumor Mutation Burden | MSI = Microsatellite Instability | MSS = Microsatellite Stable*

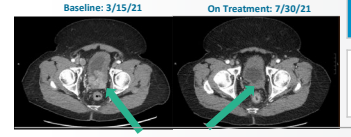
BEST TUMOR RESPONSE (N = 18)



Evaluable patients with measurable disease (not shown 11 patients with only non-target lesions)

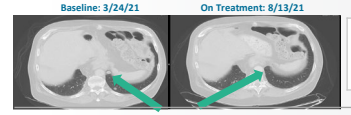
PATIENTS VIGNETTES

PATIENT 101-940
Baseline: 3/15/21 On Treatment: 7/30/21



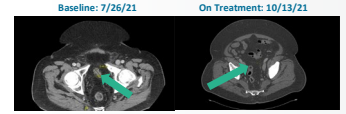
Prior Systemic Therapies	PSA ≥-50%*	RECIST 1.1 ≥-30%*	Tumor Biology
Abiraterone, enzalutamide docetaxel, cabazitaxel	-99.9%	-56% Confirmed 31-week duration	MSS

PATIENT 101-944
Baseline: 3/24/21 On Treatment: 8/13/21



Carboplatin docetaxel, cabazitaxel	0%	-74% Confirmed 25-week duration	TMB = 3 MSS PD-L1 low

PATIENT 106-959
Baseline: 7/26/21 On Treatment: 10/13/21



Abiraterone, bicalutamide, cabazitaxel, docetaxel, enzalutamide, Lupron, Olaparib	+58%	Complete reduction in soft tissue lesions, progression in bone	Unavailable

TOLERABILITY / SAFETY PROFILE

Treatment Related Adverse Events*	N = 42 n (%) Patients	
AE Preferred Term	**Any Grade**	**Grade ≥3**
Fatigue	18 (43)	
Nausea	13 (31)	
Vomiting	9 (21)	
Dizziness	8 (19)	1 (2)
White Blood Cell Count Decreased	8 (19)	1 (2)
Decreased Appetite	7 (17)	
Hypotension	7 (17)	2 (5)
Platelet Count Decreased	7 (17)	
Pruritus	7 (17)	
Anemia	5 (12)	2 (5)
Diarrhea	5 (12)	
Dry Mouth	5 (12)	
Hypoalbuminaemia	5 (12)	1 (2)
Hypothyroidism	5 (12)	

**At least possibly related to BXCL701 or pembrolizumab, occurring in >10% of patients*

- Majority of events were low grade
- AEs consistent with cytokine activation were observed—fever, myalgia, nausea, chills, fatigue, dyspnea, headache, dizziness
- SAEs experienced by 5 (12%) patients were reported as possibly related to BXCL701 or pembrolizumab: 2 reports of hypotension; dizziness; peripheral edema; pyrexia; Myasthenia Gravis; Cytokine Release Syndrome
- 2 (5%) patients discontinued therapy due to AEs
- **No evidence that BXCL701 potentiate immune-related AEs related to immune checkpoint inhibitors**

CONCLUSIONS

- In this end stage group of metastatic castration-resistant prostate cancer patients with adenocarcinoma histology, activity seen with combination of BXCL701 + pembrolizumab was highly encouraging and warrants further study:
  - Low single digit response rates expected with pembrolizumab alone in this patient population
  - Significant minority of patients in study had bone only disease, a group with very low activity to single agent pembrolizumab
  - Vast majority of study patients did not have predictive markers associated with pembrolizumab activity
- Combination of BXCL701 + pembrolizumab demonstrated manageable safety profile
  - Majority of AEs were low grade
  - No evidence of potentiation of immune-related AEs
- Biomarker work continues and will be presented in a future scientific meeting
- Study will be expanded to include randomization to combination of BXCL701 + pembrolizumab vs. BXCL701 alone

THANK YOU

BioXcel Therapeutics, Inc. would like to thank all patients, their families, and caregivers who made this study possible. BioXcel Therapeutics, Inc. 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.

CONFLICT OF INTEREST DECLARATION

Primary author Jingsong Zhang < Jingsong.Zhang@moffitt.org > is a Principal Investigator in this multicenter study sponsored by BioXcel Therapeutics, Inc. | ClinicalTrials.gov Identifier: NCT03910660