FIRST-IN-CLASS ORAL INNATE IMMUNE ACTIVATOR BXCL701 COMBINED WITH PEMBROLIZUMAB, IN PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (mCRPC) OF SMALL CELL NEUROENDOCRINE (SCNC) PHENOTYPE: PHASE 2A UPDATED INTERIM RESULTS

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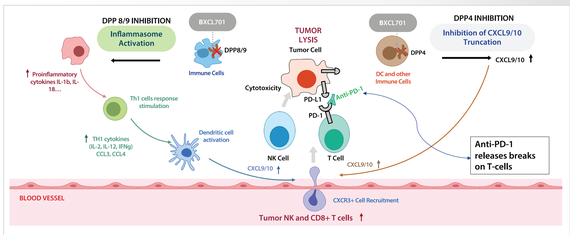
BACKGROUND

SMALL CELL NEUROENDOCRINE PROSTATE CANCER (SCNC)

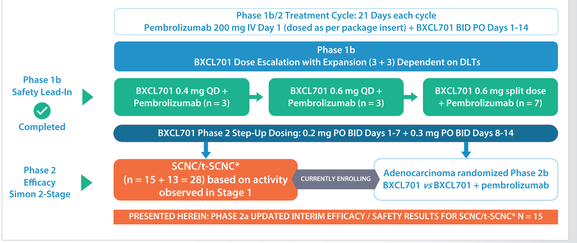
- Treatment of metastatic castration-resistant prostate cancer has evolved rapidly over the past few years:
  - 1st-line treatment with androgen deprivation therapy or one of newer androgen signaling inhibitors (ASI) abiraterone or enzalutamide followed by chemotherapy with docetaxel now standard of care
  - Docetaxel associated with median overall survival <2 years
- Treatment-emergent SCNC (t-SCNC) emerges in ~20% patients resistant to androgen receptor-targeting therapy, it is increasing due to earlier and more widespread use
- t-SCNC is a histologic subtype that morphologically resembles de novo SCNC, highly proliferative and aggressive and does not typically express androgen receptor or PSA
- There is no standard of care for SCNC or t-SCNC: by definition, cold tumors do not respond to checkpoint inhibitors (CPIs, ORR <<10%)
- BXCL701 immunomodulatory mechanism may turn a "cold" tumor micro-environment into an inflamed "hot" tumor micro-environment, contributing to overcome resistance to CPIs

BXCL701 MODULATES TUMOR MICROENVIRONMENT BY ACTIVATING INNATE IMMUNITY FOLLOWED BY ADAPTIVE IMMUNITY LEADING TO CANCER CELL DEATH AND IMPROVEMENT OF ANTI-PD-1 EFFICACY AS OBSERVED IN PRECLINICAL MODELS



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, or 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 Neuroendocrine Prostate Cancer/Treatment-emergent Small Cell Neuroendocrine Prostate Cancer

KEY INCLUSION AND EXCLUSION CRITERIA

KEY INCLUSION CRITERIA

- Histologically confirmed SCNC/t-SCNC
- Progression as defined by PCWG3 criteria
- ≥1 prior line systemic therapy for locally advanced or metastatic prostate cancer
- Serum testosterone <50 ng/dL during screening, except for those with de novo SCNC
- ECOG performance status of 0-2
- Phase 2 Efficacy Stage only:
  - ≥1 prior line chemotherapy
  - Measurable disease by RECIST 1.1

KEY EXCLUSION CRITERIA

- >2 cytotoxic chemotherapy regimens for mCRPC
- Prior treatment with anti-PD-1, anti-PD-L1, anti-programmed death-ligand 2 (PD-L2) agent or with agent directed to another co-inhibitory T-cell receptor
- History of symptomatic orthostatic hypotension within 3 months prior to enrollment

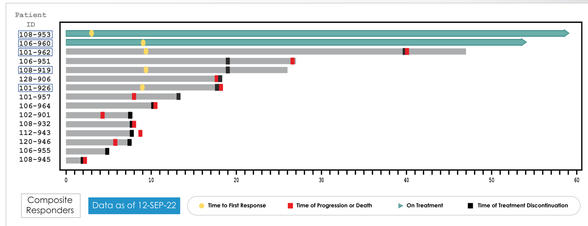
RESULTS: STUDY POPULATION

Baseline Characteristics		Enrolled Patients | SCNC/t-SCNC n = 18 (%)
Age (years)	Mean Median	67.3 SD 7.06 68.5 Range 54-78
ECOG Performance Status	0 1 2	8 (44%) 8 (44%) 2 (11%)
Bone Only disease		5 (28%)
Prior Cancer Therapies	Mean number of prior regimens	2.3 SD 1.08
Evaluable Patients		15
Prior Systemic Therapies	Previous targeted endocrine therapy *Only enzalutamide* *Only abiraterone* *No enzalutamide or abiraterone (ASI)* Platinum Chemotherapy Taxane Chemotherapy Radiation Therapy	 *1 (0.66%)* *2 (1.3%)* 12 (80%) 14 (93%) 7 (21%) 10 (66%)

Data as of 24-Nov-2021 unless noted otherwise

EXPOSURE DURATION AND SUBJECT DISPOSITION

15 EVALUABLE PATIENTS PREVIOUSLY REPORTED AT ASCO GU



RESULTS: STUDY POPULATION

Data cut-off date 12-SEP-22

Best Response	SCNC/t-SCNC Evaluable Patients n = 15 (%) [95% Exact CI]
Composite Response	5 (33%) [11.8 – 61.6]
Best RECIST 1.1 Response by Investigator Assessment	
RECIST Evaluable[a]	12 (80%)
Partial Response	4 (33%) [9.9 – 65.1]
Confirmed PR	*3 (75%)*
Unconfirmed PR	*1 (25%)*
SD (any duration) including Minor Response	3 (27%)
Non-CR / Non-PD	7 (58%)
PD	5 (41%)
Disease Control Rate (CR + PR + SD)	58%
CTC[b]	
CTC Evaluable[c]	3
CTC Response[d]	1 (33%)
PSA	
PSA Evaluable [e]	14 (100%)
PSA_{50} Response	1 (7%) [0.2– 33.9]

Composite response rate: 33%
- RECIST-defined PR*: 33%
- Disease control rate: 58%
- CTC response: 33%

Patients typically tend not to be PSA secretors
- PSA50: 1%—1 patient with -73% PSA decrease lasting for almost a year

**Includes confirmed and unconfirmed PRs*

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

EFFICACY UPDATE: RESPONDERS

DATA AS OF 11-OCT-22

Median Duration of Treatment = 47 weeks | Median Duration of Response = 39 weeks

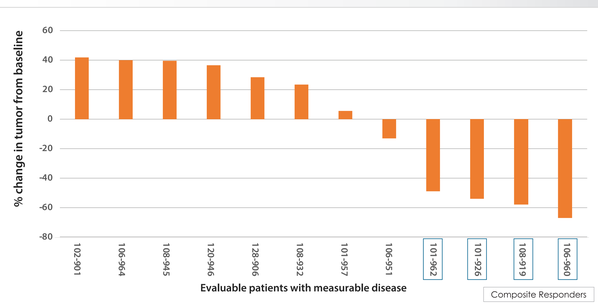
Patient	Prior Systemic Therapies	Duration on Treatment	RECIST 1.1 ≥-30%* DOR	CTC ≥5/7.5 ml to <5/7.5 ml*	PSA ≥-50%* DOR	Tumor Biology
106-960	Bicalutamide, Lupron carboplatin, etoposide	55 weeks	-67% Confirmed 46 weeks		NA	TMB = 3 MSS
108-919	Degarelix, Lupron	19 weeks (+18 off treatment)	-58% Confirmed 26 weeks		NA	TMB = 0 MSS
101-926	Abiraterone, leuprolide, chemoradiation, abiraterone, prednisone, cisplatin, etoposide	18 weeks	-54% Unconfirmed 9 weeks	1 to 0	NA	MSS
101-962	ADT, carboplatin / docetaxel	47 weeks	-48.6% Confirmed 39 weeks		NA	TMB = 4 Microsatellite Status not determined
108-953	Degarelix, Lupron, carboplatin/docetaxel	59 weeks	Unavailable	19 to 4	-73% 50 weeks	MSS PD-L1 low

On Treatment | Off Treatment | Response

*Change from baseline | DOR = Duration of Response | TMB = Tumor Mutation Burden | MSS = Microsatellite Stable

BEST TUMOR RESPONSE (N = 12)

DATA AS OF 11-OCT-22



TOLERABILITY / SAFETY PROFILE

Treatment Related Adverse Events*	n = 18 n (%) Patients Reporting AE	
AE Preferred Term	Any Grade	Grade ≥3
Fatigue	6 (33)	
Hypotension	4 (22)	1 (6)
Cough	3 (17)	
Nausea	3 (17)	
Pruritus	3 (17)	
Acute Kidney Injury (AKI)	2 (11)	2 (11)
Diarrhoea	2 (11)	
Dry Mouth	2 (11)	

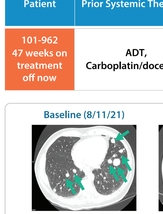
**At least possibly related to BXCL701 or pembrolizumab, occurring in >10% of patients*

- Majority of events were low grade
- AEs consistent with cytokine activation were observed—fever, nausea, chills, fatigue, headache, dizziness
- SAEs experienced by 3 (17%) patients were reported as possibly related to BXCL701 or pembrolizumab:
  - 1 patient hospitalized for Grade 1 orthostatic hypotension
  - 1 patient with Grade 3 hypotension and AKI (resolved)
  - 1 patient with AKI and Grade 5 Tumor Lysis Syndrome
- 4 (22%) patients discontinued therapy due to AEs
- No evidence that BXCL701 potentiates immune-related AEs related to immune checkpoint inhibitors

PATIENT VIGNETTE: PATIENT 101-962

Patient	Prior Systemic Therapies	RECIST 1.1 ≥-30%* DOR
101-962 47 weeks on treatment off now	ADT, Carboplatin/docetaxel	-48.6% Confirmed 39 weeks

Baseline (8/11/21) | Post C6 (1/4/22)



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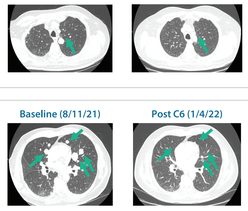

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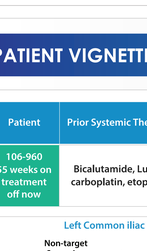

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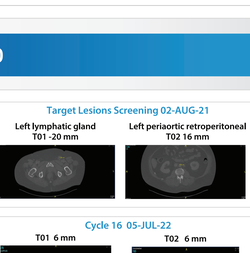

PATIENT VIGNETTE: PATIENT 106-960

Patient	Prior Systemic Therapies	RECIST 1.1 ≥-30%* DOR
106-960 55 weeks on treatment off now	Bicalutamide, Lupron carboplatin, etoposide	-67% Confirmed 48 weeks

Target Lesions Screening 02-AUG-21

Left lymphatic gland T01 -20 mm | Left periaortic retroperitoneal T02 16 mm

Left Common iliac Lymph node

Non-target | Non-target Cycle 16

Cycle 16 05-JUL-22

T01 6 mm | T02 6 mm

CONCLUSIONS

- BXCL701 + pembrolizumab showed highly encouraging and durable response rates in SCNC, for which there is no standard of care
  - All responders were MSS and/or TMB low
- 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 continues to enroll patients to completion as per protocol

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 Vince O'Neill < voneill@BioXcelTherapeutics.com > is Head of Oncology Unit at BioXcel Therapeutics, Inc., which sponsors this multicenter study

ClinicalTrials.gov Identifier: NCT03910660

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