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Twenty-Sixth Annual
Prostate Cancer Foundation
SCIENTIFIC RETREAT

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BXCL701 (an Innate Immune Activator) in Combination with Pembrolizumab in Patients with Small Cell Neuroendocrine Prostate Cancer (SCNC; NEPC)

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bioxcel therapeutics

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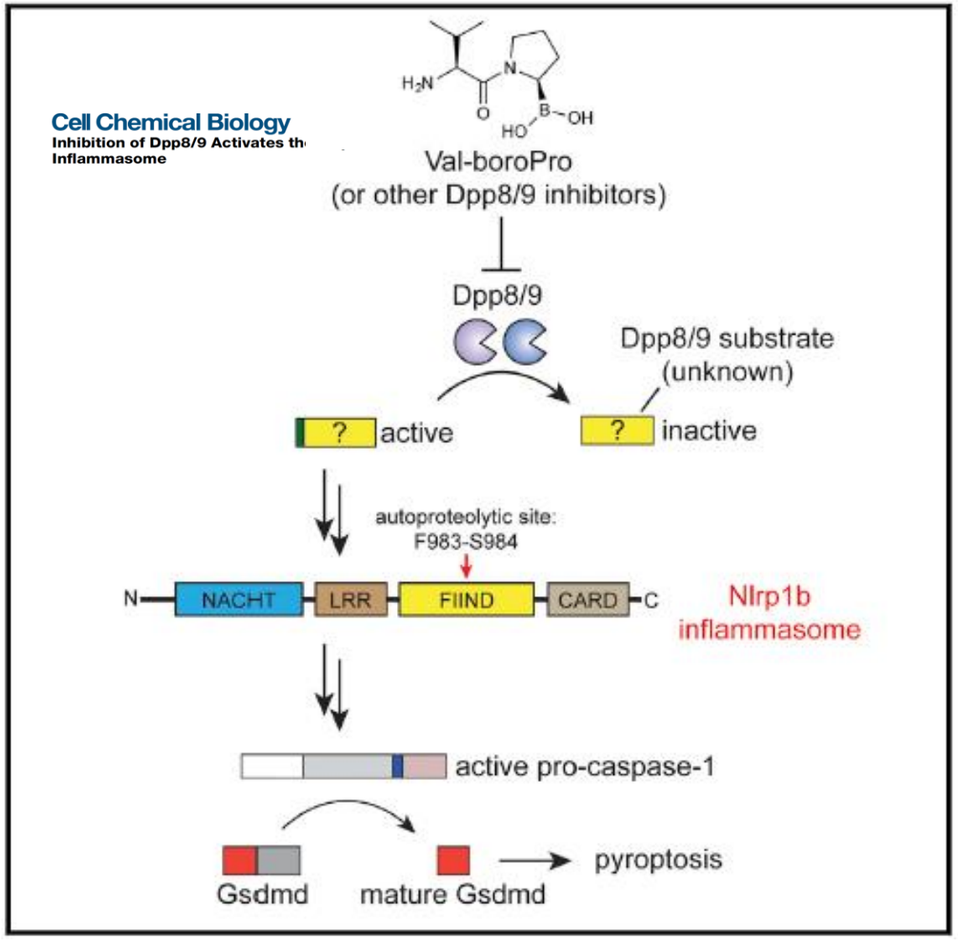
Conflicts of Interest

- I am an employee of BioXcel Therapeutics
- I own stock in BTAI

BXCL701 (Talabostat) Overview

Drug Candidate	• BXCL701 (talabostat): Orally administered activator of systemic innate immunity pathway • RP2D 0.6mg od
Function/MoA	• Dual MoA: – DPP (dipeptidyl peptidases) inhibitor: DPP8/9, FAP – Innate Immune Activation and Inhibition of Immune Evasion
Initial Indications	• Neuroendocrine Prostate Cancer and Pancreatic Cancer in combination with CPIs/ IO agents
Development	• Demonstrated clinical proof of mechanism & tolerable safety profile (>700 patient data) • Single-agent anti-tumor activity seen in metastatic melanoma • Trials in Prostate and Pancreatic Cancer

Macrophage Pyroptosis is the Central Component of the Activity of BXCL701 Through DPP8/9 Inhibition



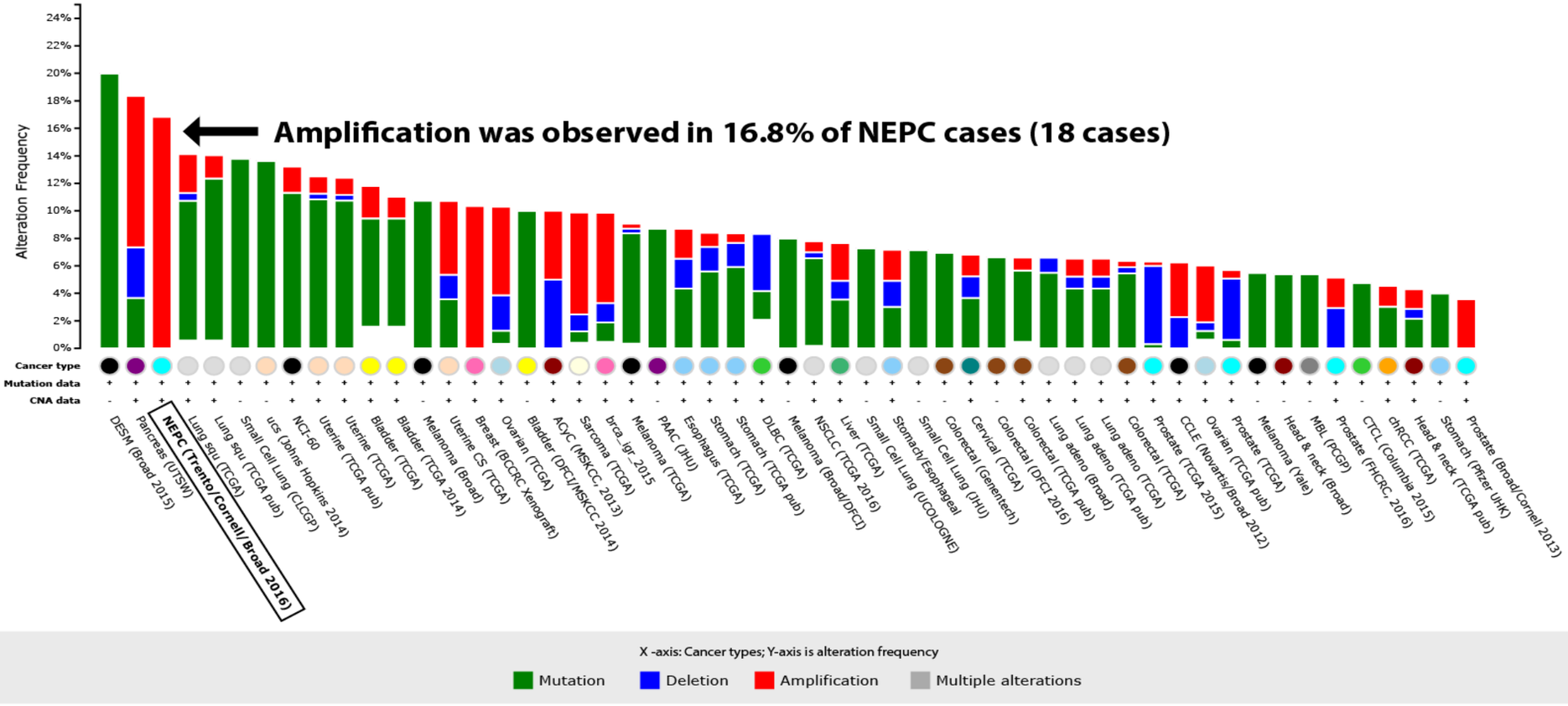
- Inhibition of DPP8/9 activates the pro-inflammatory process of pyroptosis in macrophages
- Macrophage pyroptosis through the Nlrp1b pathway drives the activation of caspase-1 and subsequent activation of pro-IL-1β and pro-IL-18 leading to the production of a host of other cytokines
- Mouse genetics further supports this process as the driver of BXCL701 activity

Okondo MC etal. Cell Chem Biol. 2018

Frequency of Target Alteration Across Tumor Types

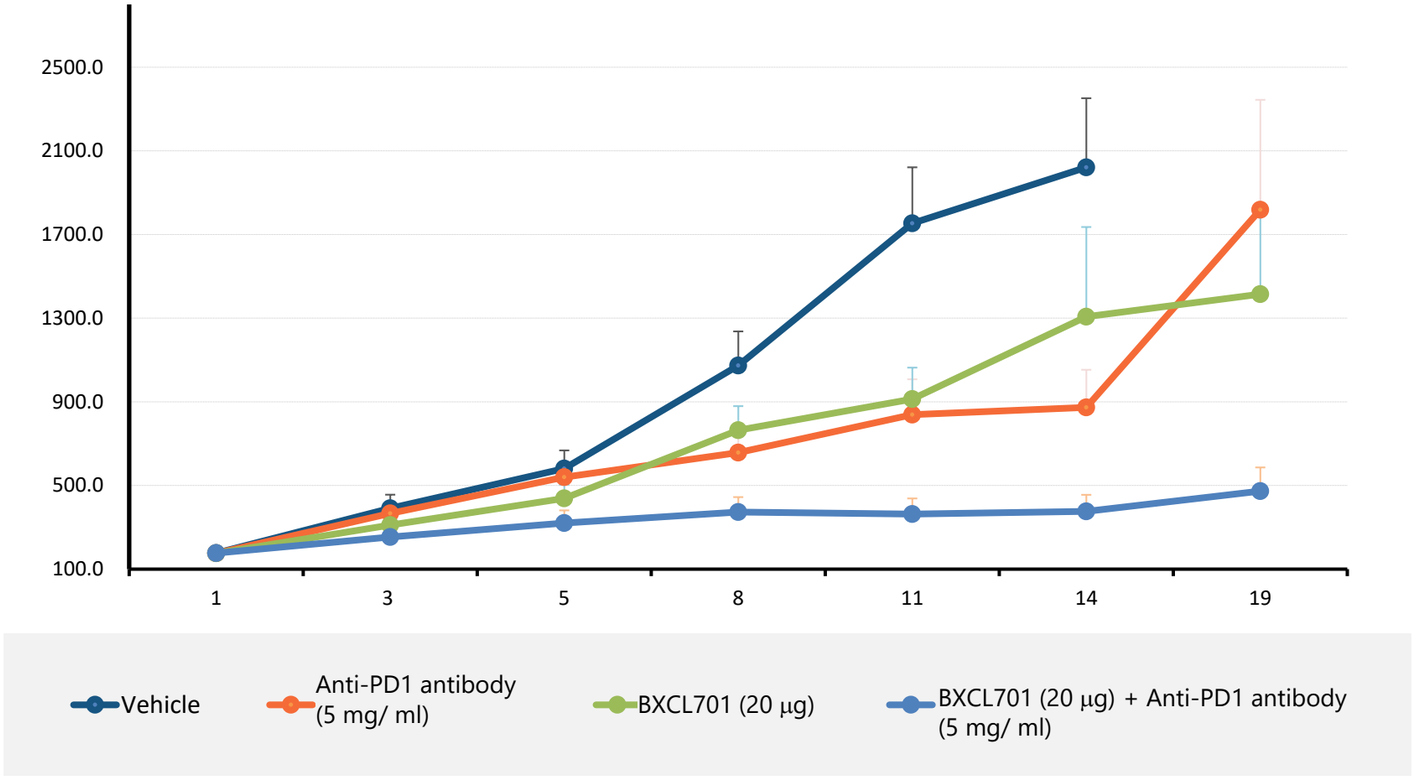
An analysis of genomic alterations in FAP, DPP8 and DPP9 across cancer genomic profiles of 33172 patients from 150 different cancer studies included dataset from TCGA at cBioPortal

AACR2017 - Abstract 2629



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#
- 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**

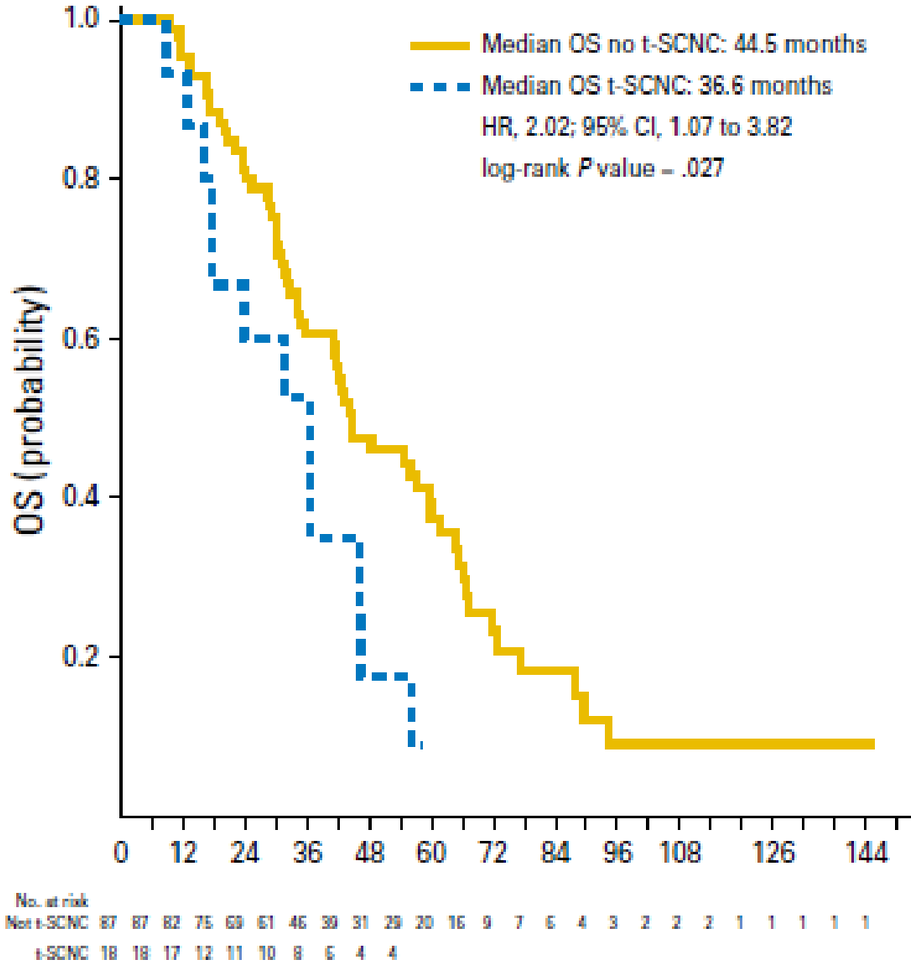
AACR2017 Abstract 2629

Prior Clinical Safety Evaluations for BXCL701

- BXCL701 has been administered to more than 700 human subjects in Phase 1-3 clinical trials as single agent or in combination with chemotherapy
- BXCL701 was generally well tolerated with the most frequently observed AEs of:
  - Edema/peripheral swelling
  - Fever and rigors- events consistent with cytokine up-regulation
  - Dizziness
- Other AEs commonly reported across studies include:
  - Nausea, vomiting
  - Rash (10%)- usually described as not otherwise specified, erythematous or popular
  - Hypotension - uncommon
- These events, including edema, tend to be manageable and reversible and usually resolve following a drug hold

De novo Or Treatment-emergent Small-Cell / Neuroendocrine Prostate Cancer: A High Unmet Medical Need

- *De Novo* small-cell cancer of the prostate is present in <1% of newly diagnosed cases, associated with AR-null phenotype and progression with low serum PSA levels
- Treatment-emergent SC/NEPC may reflect a trans-differentiation process after androgen-ablating therapy
- Both *de novo* and treatment-emergent SC/NEPC are highly aggressive forms of prostate cancer with no current standard of care



Aggarwal R, et al. JCO 2018

Phase 1b/2: Key Study Objectives & Inclusion/Exclusion Criteria

PRIMARY OBJECTIVE

- Estimate the composite response rate in patients with SCNC
- Composite response rate is defined as achieving 1 or more of the following:
  - Objective response by Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 criteria
  - Circulating tumor cell (CTC) conversion from >5/7.5 mL to <5/7.5 mL per Veridex assay by Week 12
  - Greater than 50% PSA decline from baseline by Week 12 of protocol therapy

KEY SECONDARY OBJECTIVES

- Radiographic progression-free survival (rPFS) in patients with SCNC
- PSA progression-free survival (PSA PFS) in patients with SCNC
- Overall survival (OS) in patients with SCNC
- Duration of response (DOR) in patients with SCNC
- Further characterize the safety profile of the combination
- Assess the pharmacokinetics of BXCL701 using sparse PK sampling
- Assess the pharmacodynamic profile of the combination by measuring relevant effects on those cytokines previously shown to be modulated by BXCL701 in humans

KEY INCLUSION CRITERIA

- Patient has progressive, metastatic castration-resistant disease, as defined by PCWG3 criteria
- Progression during or following completion of at least 1 prior line of systemic therapy for locally advanced or metastatic prostate cancer
- Efficacy Stage only:
  - Evidence of SCNC on central pathology review of archival tumor tissue
  - Received at least 1 prior line of chemotherapy
  - Willing to undergo metastatic tumor biopsy during Screening.
- Serum testosterone <50 ng/dL during Screening except for those with de novo small cell prostate cancer
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-2

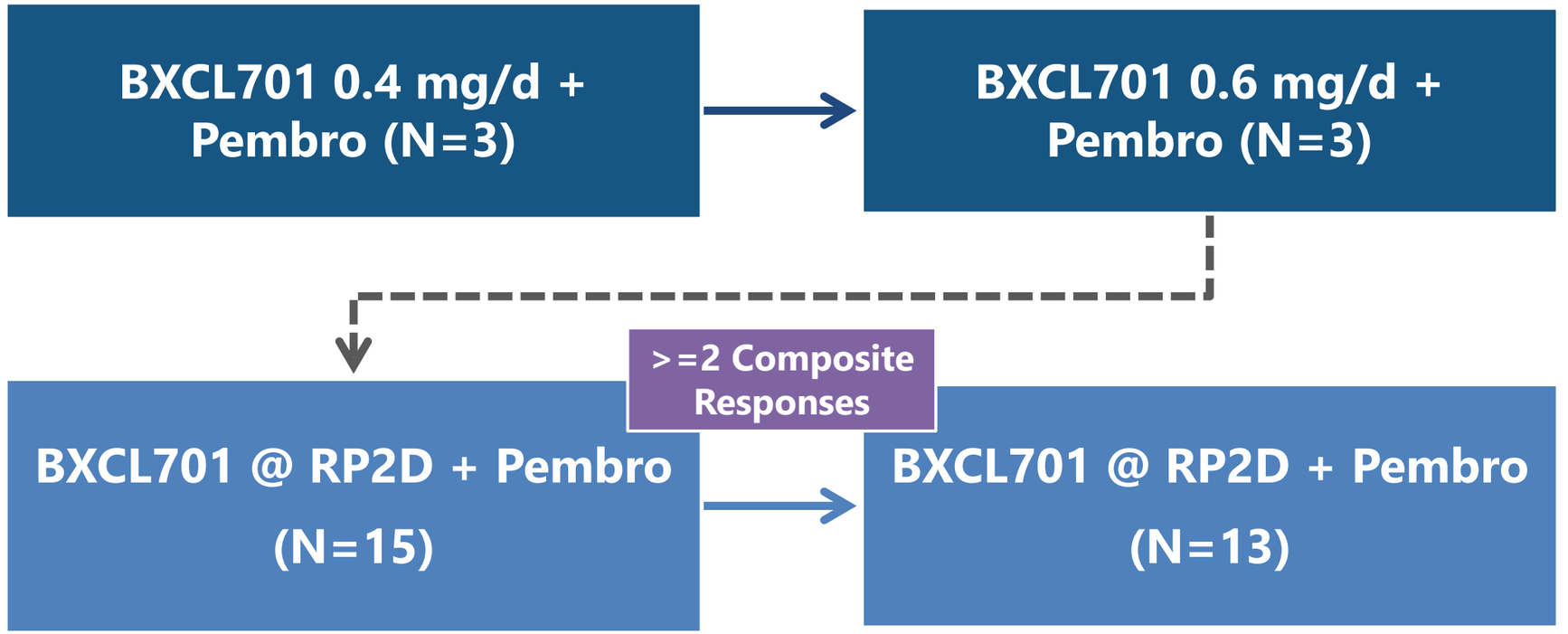
KEY EXCLUSION CRITERIA

- Has received treatment with >2 cytotoxic chemotherapy regimens for CRPC
- 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

Trial Schematic

Safety Lead-In
Standard 3X3 dose escalation with expansion dependent on DLTs.

Efficacy Stage
Simon 2 stage
Power: 0.8,
Type 1 error:0.05;
P0:15%, P1:35%



Treatment Cycle: BXCL701 qd PO days 1-14 of 21 days
Pembrolizumab 200mg IV Q21 days

Phase 1b/2: Current Status

- Study Sites located in US and UK
  - Lead PIs: R. Aggarwal and J. DeBono
- Cohort 1: Enrollment and DLT evaluation period complete
- Cohort 2: Pembro + BXCL701 0.6mg qd
  - Expected completion of DLT evaluation period by end November.
  - Next Steps:
    - If 0 patients with DLT, begin Phase 2 efficacy portion.
    - If ≥1 of 3 patients with DLT, further dose exploration at current dose level with additional 6-9 pts.
- Current data-cut: Cohort 1- 10/16/2019

Phase 1b – Safety Lead-In
Patient Disease History

Disease History		No. of Subjects	
		BXCL701 0.4mg + Pembro (N=3)	BXCL701 0.6mg + Pembro (N=2)
Most Recent Histopathology	Adenocarcinoma	3	1
	Adenocarcinoma with small-cell or neuroendocrine features	-	1
	Primary Small cell or neuroendocrine carcinoma	-	-
Prior Systemic Therapies	ADT therapy	3	2
	Chemotherapy	3	1
	Radiotherapy	2	2
Type of Progression at Study Entry	PSA only	1	-
	Bone +/- PSA	1	1
	Bone + nodal disease +/- PSA	1	-
	Visceral +/- other	-	1

Phase 1b – Safety Lead-In
Early Safety Summary

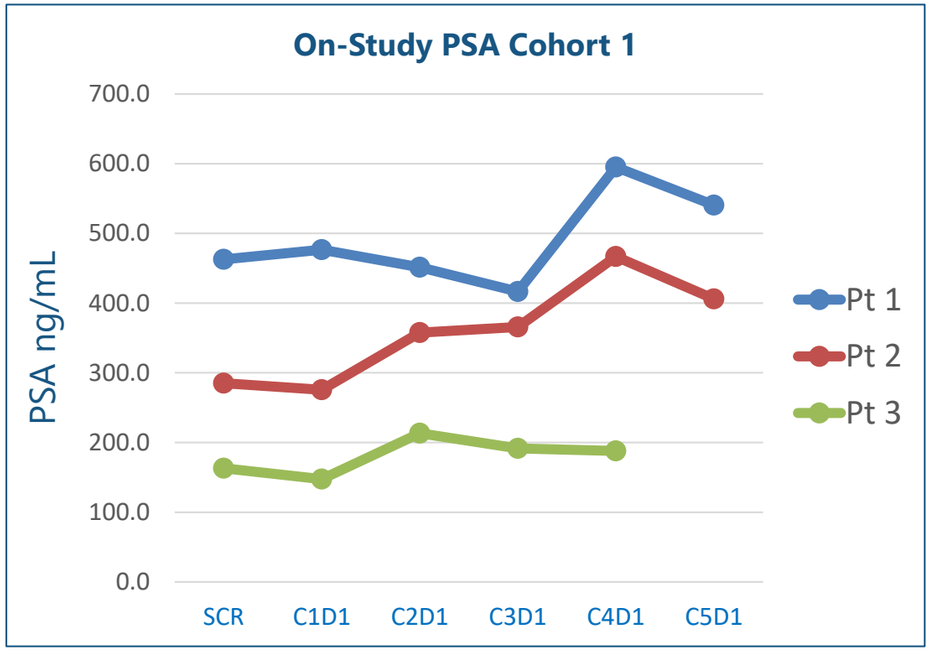
Safety	No. of Patients
	BXCL701 0.4mg + Pembro (N=3)
Any DLT	0
Any treatment-related SAE	0
Any Cause AE	3
Any BXCL701 treatment-related AE*	2
Any Pembro treatment-related AE*	2
Any BXCL701 or Pembro treatment-related Grade 3 or 4 AE	1**
Common treatment related AEs (>1 pt) - Hypocalcemia	2

**Includes possibly-related events*
***Grade 3 thrombocytopenia requiring transfusion*

Phase 1b – Safety Lead-In
Disease Status

Composite Responses	BXCL701 0.4mg + Pembro (N=3)
RECIST Response after 3 cycles (9 weeks) per Investigator - SD - Non-CR/Non-PD	 2 1*
CTC conversion from >5/7.5 to <5/7.5 by Week 12	Data not yet available
PSA decline >50% by Week 12	0

**Pt #3 with only bone mets at baseline*



BXCL701-201 Summary

- BXCL701 is an investigative orally available innate immune activator and inhibitor of immune evasion
- BXCL701 has demonstrated a safety profile, based on 700 subject database
  - Has been generally well tolerated, with manageable and usually transient side effects
- In the Phase 1b safety lead-in portion of this study in subjects with mCRPC:
  - BXCL701 + pembro safety has been demonstrated in the initial cohort with no SAEs or DLTs
  - Assessment of BXCL701 + pembro combination safety is ongoing at the final dose escalation cohort
  - Preliminary pharmacokinetics of BXCL701 are within expectations based on prior data
  - All subjects remain on treatment
- The Phase 2 portion of this study will be limited to subjects with SC/NEPC and will assess the anti-tumor activity of the combination of BXCL701 + pembro in a setting where checkpoint inhibitor monotherapies have demonstrated limited clinical benefit

Thank You

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