BXCL701, FIRST-IN-CLASS ORAL ACTIVATOR OF SYSTEMIC INNATE IMMUNITY PATHWAY COMBINED WITH PEMBROLIZUMAB (KEYTRUDA), IN MEN WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (mCRPC): PHASE 2 RESULTS

e-Poster 610P

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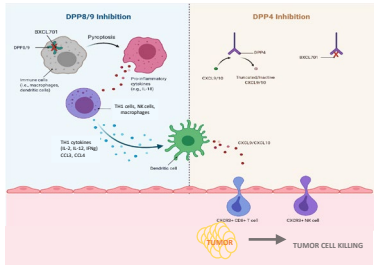
Background

Metastatic Castration Resistant Prostate Carcinoma (mCRPC)

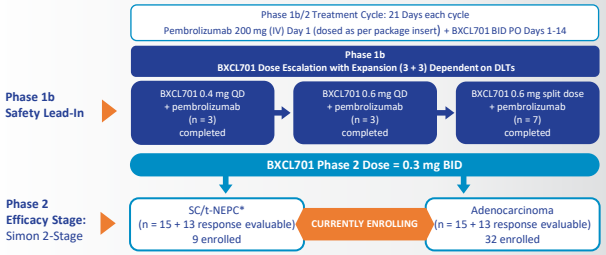
- 248,530 new cases of prostate cancer in US in 2021 *(American Cancer Society estimates)*
- 10–20% develop CRPC within ~5 years of follow-up, most of them having metastases at time of diagnosis
- Treatment of mCRPC has evolved rapidly over the past few years:
  - 1st-line treatment with androgen deprivation 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 *(KEYNOTE-199 ASCO-GU 2020)*
  - Single agent objective response rate ~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

MOA: BXCL701 Modulates the Tumor Microenvironment by First Activating the Innate and Then the Adaptive Immunity Leading to Cancer Cell Death



- DPP8/9 inhibition by BXCL701 activates inflammasome-mediated pyroptosis to alert and prime cells in the adaptive immune system
- Inflammasome activation mediates proinflammatory cytokine release, which in turn results in the TH1 response and release of the chemokines
- This results in activation of Dendritic Cells, which activate CXCR3+ Natural Killer and CD8+ T cells through chemokine release
- DPP4 inhibition increases tumor content of CXCL9/10, which recruits CXCR3+ NK and T cells
- The increase of the immune cell content in the tumor microenvironment suggesting that BXCL701 can enhance immunotherapy efficacy in 'cold' tumor types

Methods | Trial Schematic and Key Objectives



PRESENTED HEREIN: PHASE 2 PRELIMINARY EFFICACY AND SAFETY RESULTS FOR ADENOCARCINOMA

Primary objective for each Phase 2 Cohort: Composite Response Rate Target >15%
Need >2 composite responses to proceed to Stage 2
Additional objectives: DoR, PFS, changes in circulating cytokines and correlation of outcome with baseline tumor characteristics

*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 Group (ECOG) performance status of 0-2
- Phase 2 Efficacy Stage only:
  - **For Cohort A (SC/t-NEPC):**
    - 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 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
- Brain metastases that are symptomatic and progressive on imaging
- Significant cardiovascular or pulmonary disease
- History of symptomatic orthostatic hypotension within 3 months prior to enrollment

See ClinicalTrials.gov Identifier: NCT03910660 for more details

Phase 1b Results Support BID Dosing of BXCL701 in Combination With 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 (BID) and escalating to the maximum 0.6 mg daily dose in week 2 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

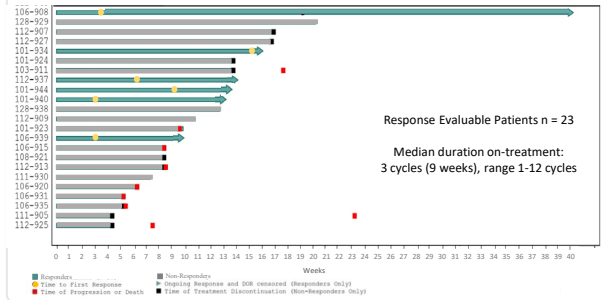
Presented at ASCO GU 2021 Poster 124

Results: Study Population

Data as of 08-JUL-21 unless noted otherwise

Baseline Characteristics		Phase 2 Adenocarcinoma Cohort | N (%)
Enrolled		32
Age (years)	Mean (range)	68.2 (51-82)
ECOG Performance Status	0 1 2	12 (38) 19 (59) 1 (3)
Bone Only disease		14 (44)
Prior Cancer Therapies	Mean number of prior regimens (SD)	5.3 (2.35)
Prior Systemic Therapies	2nd Generation ASI *1 ASI* *2 ASI*	31 (97) *12 (37)* *19 (59)*
	Taxane Chemotherapy	32 (100)
	Provenge (sipuleucel-T)	10 (31)
	Radiation Therapy	6 (19)

Exposure Duration and Subject Disposition



Preliminary Activity Observed in mCRPC Population

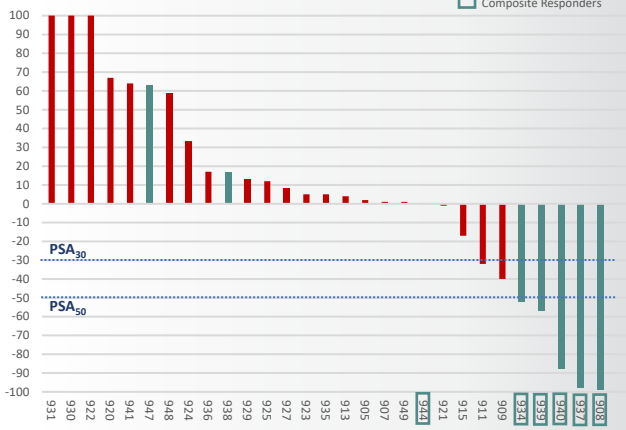
Best Response	Phase 2a Adenocarcinoma Patients n (%)
RECIST 1.1 by Investigator Assessment[a]	
RECIST Evaluable	19
Best RECIST Response	
Confirmed PR	1 (5)
Unconfirmed PR	2 (11)
SD (any duration) including Minor Response	8 (42)
Non-CR / Non-PD	1 (5)
PD	7(37)
Disease Control Rate (PR + SD + Non-CR / Non-PD)	12 (63)
PSA	
PSA Evaluable[b]	29[c]
PSA_{50} Response	5 (17)
CTC[d]	
CTC Evaluable[e]	8
CTC Response[f]	2 (25)
Composite Response n = 23	6 (26)

Composite response rate is 26%:
- RECIST-defined PR is 16%
- Disease control rate (PR + SD + non-CR / non-PD) is 63%
- PSA_{50} is 17% including 3 patients who had a PSA decrease around 90%
- CTC response is 25%

CTC data cut-off MAY-21
RECIST 1.1 / PSA data cut-off 23-AUG-21

[a] Patients who received ≥2 cycles of study therapy and 1 on-treatment tumor assessment [b] Baseline value >4 ng/mL and one on-treatment PSA assessment [c] 23 patients evaluable for composite response [d] Circulating tumor cell [e] Baseline CTC value ≥5/7.5 mL and one measurable on-treatment assessment [f] CTC conversion from ≥5/7.5 mL to <5/7.5 mL

Adenocarcinoma PSA Responses



Summary of Composite Responses

Patient	Prior Systemic Therapies	PSA ≥-50%*	CTC ≥5/7.5 ml to <5/7.5 ml*	RECIST 1.1 ≥-30%*	Tumor Biology
106-908	Enzalutamide, sipuleucel-T docetaxel, cabazitaxel	-99%	5 to 0	-60% (confirmed)	TMB = 20.7 MSI-high /unstable PD-L1 low
101-934	Nilutamide, abiraterone enzalutamide, sipuleucel-T docetaxel, cabazitaxel	-52%	Baseline CTC = 0	-19%	TMB = 2 MSI stable PD-L1 low
112-937	Abiraterone, sipuleucel-T docetaxel	-98.5%	▪	-24%	TMB = 1 MSI stable
106-939	Abiraterone, enzalutamide docetaxel, cabazitaxel	-57%	26 to 1	-15%	Data pending
101-940	Abiraterone, enzalutamide docetaxel, cabazitaxel	-99.9%	▪	-52% (unconfirmed)	MSI stable
101-944	Carboplatin docetaxel, cabazitaxel	0%	3 to 2	-55% (unconfirmed)	TMB = 3 MSI stable PD-L1 low

*change from baseline ▪ Sampling error Response TMB = Tumor Mutation Burden | MSI = Microsatellite Instability

Phase 2 Safety in Adenocarcinoma Population

Treatment Emergent Adverse Events	N = 32 n (%)			
Subjects with any TEAE	27 (84)			
AE related to BXCL701 or pembrolizumab	10 (31)			
SAE related to BXCL701 or pembrolizumab	2 (6)			
AE Preferred Term	**Grade 1**	**Grade 2**	**Grade 3**	**Total**
Fatigue	3	2	-	5
Hypotension*	3	1	-	4
Pruritus and Rash	4	-	-	4
Dizziness	2	-	1	3
Arthralgia/Myalgia	-	2		2
Oedema peripheral	1	-	-	1
Dehydration		1	-	1
Vomiting	-	1	-	1
Decreased appetite	1	-	-	1
Decreased lymphocyte count	-	1	-	1
Blood lactic acid increased	1	-	-	1
Pyrexia	1	-	-	1
Cytokine Release Syndrome	-	1	-	1

*Includes orthostatic hypotension

- All events ≥3% reported
- 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
- No evidence that BXCL701 potentiate immune-related AEs related to immune checkpoint inhibitors

Conclusions

- 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 follow-up in the Phase 2 portion of the study at this data cut-off:
    - **6** patients in the adenocarcinoma cohort have achieved a composite response
    - All responders experienced a decrease in tumor size from baseline
    - **4** responders were Microsatellite Stable, **1** long term responder showed High Microsatellite Instability
    - Retrospective analysis to identify a potential biomarker is planned
- BXCL701 BID dosing schedule continues to demonstrate an acceptable tolerability when given in combination with pembrolizumab:
  - Primarily low grade on-target adverse events consistent with cytokine activation
- This study continues to enroll patients to completion as per protocol
- Results to date compare favorably to single agent pembrolizumab despite a more heavily pretreated population (KEYNOTE-199)

THANK YOU

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