BIOXCEL THERAPEUTICS, INC.

TITLE: A Phase 1b/2 Study of BXCL701, a Small Molecule Inhibitor of Dipeptidyl Peptidases (DPP), Administered in Combination with the Anti-Programmed Cell Death 1 (PD-1) Monoclonal Antibody Pembrolizumab (PEMBRO; Keytruda®) in Patients with mCRPC either Small Cell Neuroendocrine Prostate Cancer (SCNC; NEPC) or Adenocarcinoma Phenotype

PROTOCOL NUMBER:	**BXCL701-201**
STUDY DRUG:	**BXCL701 (Talabostat)**
IND:	**130735**
SPONSOR:	**BioXcel Therapeutics, Inc.** 555 Long Wharf Drive New Haven, CT 06511 | USA

DATE OF ORIGINAL PROTOCOL:	**24 September 2018**
DATE OF AMENDMENT 1:	**31 October 2018**
DATE OF AMENDMENT 2:	**27 February 2019**
DATE OF AMENDMENT 2a (UK Only):	**08 May 2019**
DATE OF AMENDMENT 3:	**20 December 2019**
DATE OF AMENDMENT 3a: (UK Only):	**29 April 2020**
DATE OF AMENDMENT 4:	**15 June 2020**
DATE OF AMENDMENT 5:	**26 August 2020**
DATE OF AMENDMENT 6:	**16 October 2020**
DATE OF AMENDMENT 7:	**10 August 2021**

24-HOUR SAE PHONE NUMBER:	[redacted] (US Toll-Free: [redacted]
MEDICAL MONITOR:	[redacted] [redacted] IQVIA Biotech Phone: [redacted] Mobile: [redacted] E-mail: [redacted]

CONFIDENTIAL INFORMATION
The information contained in this document is the property of BioXcel Therapeutics, Inc. (or under its control), and therefore provided to you in confidence as an investigator, potential investigator or consultant, for review by you, your staff and an applicable Independent Ethics Committee/Institutional Review Board. It is understood that this information will not be disclosed to others without written authorization from BioXcel Therapeutics Inc, except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

A PHASE 1B/2 STUDY OF BXCL701, A SMALL MOLECULE INHIBITOR OF DIPEPTIDYL PEPTIDASES (DPP), ADMINISTERED IN COMBINATION WITH THE ANTI-PROGRAMMED CELL DEATH 1 (PD1) MONOCLONAL ANTIBODY PEMBROLIZUMAB (PEMBRO; KEYTRUDA®) IN PATIENTS WITH MCRPC EITHER SMALL CELL NEUROENDOCRINE PROSTATE CANCER (SCNC; NEPC) OR ADENOCARCINOMA PHENOTYPE

Key Sponsor Personnel

[redacted]
[redacted]
BioXcel Therapeutics, Inc
Phone: [redacted]
Email: [redacted]

[redacted]
[redacted]
BioXcel Therapeutics, Inc.
Phone: [redacted]
E-mail: [redacted]

[redacted]
[redacted]
BioXcel Therapeutics, Inc.
Phone: [redacted]
E-mail: [redacted]

PROTOCOL AMENDMENT 7 SIGNATURE PAGE

BioXcel Therapeutics Inc. Protocol BXCL701-201

A PHASE 1B/2 STUDY OF BXCL701, A SMALL MOLECULE INHIBITOR OF DIPEPTIDYL PEPTIDASES (DPP), ADMINISTERED IN COMBINATION WITH THE ANTI-PROGRAMMED CELL DEATH 1 (PD-1) MONOCLONAL ANTIBODY PEMBROLIZUMAB (PEMBRO; KEYTRUDA®) IN PATIENTS WITH MCRPC EITHER SMALL CELL NEUROENDOCRINE PROSTATE CANCER (SCNC; NEPC) OR ADENOCARCINOMA PHENOTYPE

By signing below, the investigator agrees to adhere to the protocol as outlined and agrees that any changes to the protocol must be approved by BioXcel Therapeutics, Inc prior to seeking approval from the Institutional Review Board (IRB) and/or Independent Ethics Committee (IEC).

This study will be conducted in accordance with current United States Food and Drug Administration (FDA) regulations, International Council for Harmonization (ICH) Guidelines, Good Clinical Practice (GCP), the ethical principles that have their origins in the Declaration of Helsinki, and local ethical and legal requirements.

Principal Investigator (PI): _____

Name of Institution: _____

Address: _____

_____

Phone Number: _____

PI Signature: _____

Date: _____

Sponsor Signature: [redacted] te: 16-Aug-2021

PROTOCOL SYNOPSIS

Name of Sponsor:

BioXcel Therapeutics, Inc.

Name of Investigational Product:

BXCL701 (talabostat mesylate); valine-proline boronic acid formulated as the methanesulfonate salt.

Name of Active Ingredient:

(2R)-1-[(2S)-2-amino-3-methyl-1-oxobutyl]-2-pyrrolidinyl]boronic acid, methanesulfonate salt.

Title of Study:

A Phase 1b/2 Study of BXCL701, a Small Molecule Inhibitor of Dipeptidyl Peptidases (DPP), Administered in Combination with the Anti-Programmed Cell Death 1 (PD-1) Monoclonal Antibody Pembrolizumab (PEMBRO; Keytruda®) in Patients with mCRPC either Small Cell Neuroendocrine Prostate Cancer (SCNC; NEPC) or Adenocarcinoma Phenotype.

Study Phase:

Phase 1b/2

Study Center(s):

10-20 study centers.

Study Objectives:

The purpose of the study is to assess the safety and efficacy of BXCL701 monotherapy and in combination with pembrolizumab (PEMBRO; Keytruda) in patients with metastatic Castrate-Resistant Prostate Cancer (mCRPC), either Small Cell Neuroendocrine (SCNC) or Adenocarcinoma Phenotype.

In the Phase 1b portion, increasing dose levels of BXCL701 will be explored sequentially in patients with mCRPC regardless of histology.

In the Phase 2a portion of the study, patients will be grouped in 1 of 2 cohorts based on histopathology:

- Cohort A: Patients with any SCNC histopathological features, either de novo or treatment-emergent including mixed SCNC.
- Cohort B: Patients with adenocarcinoma and no evidence of small cell or neuroendocrine features on recent histopathology.

If a given cohort shows preliminary efficacy in the Phase 2a, then the Phase 2b portion of the study will evaluate the histologic subtype in a randomized proof-of-concept study. The description that follows is applicable for the subtype(s) warranting further evaluation in the Phase 2b portion.
Patients with SCNC (i.e., those who meet Cohort A disease criteria) will be randomized 2:1 to receive BXCL701 combined with PEMBRO or BXCL701 monotherapy. Similarly, patients with adenocarcinoma (i.e., those who meet Cohort B disease criteria) will be randomized 2:1 to receive BXCL701 combined with PEMBRO or BXCL701 monotherapy. In either cohort, crossover to combination treatment is permissible upon radiographic disease progression in the monotherapy arm. For a given histologic subtype (SCNC or adenocarcinoma), the purpose of the Phase 2b component is to estimate efficacy outcomes in each treatment group, with the BXCL701 monotherapy arm serving as an internal reference group; the two treatment groups will not be formally compared. In addition, the total experience for patients within the mCRPC histologic subtype from the Phase 2a and Phase 2b components will collectively provide greater precision in relation to the efficacy and safety of the combination regimen.

The objectives below will apply to the Phase 2a and 2b portions of the study and will be assessed with descriptive analyses. Because of the more aggressive nature of the disease for patients in Cohort A (SCNC), the primary and secondary efficacy objectives will be assessed separately by histologic subtype.

Primary Objectives:

Phase 2a primary objectives

- To estimate the composite response rates (CRR) of the combination of BXCL701 + PEMBRO in Cohort A and B, respectively. CRR 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
  - 50% or greater PSA decline from baseline.

Phase 2b primary objective

- To evaluate the response rates, defined by RECIST 1.1 criteria, by histologic subtype in patients treated with the combination of BXCL701 + PEMBRO and with BXCL701 monotherapy.

Secondary Objectives

The secondary objectives of the Phase 2a study are:

- To estimate the median radiographic progression-free survival (rPFS) of the combination of BXCL701 and PEMBRO in Cohort A and B.
- To estimate the median PSA progression-free survival (PSA PFS) of the combination of BXCL701 and PEMBRO in Cohort A and B.
- To estimate the median overall survival (OS) of the combination of BXCL701 and PEMBRO in Cohort A and B.
- To estimate the median duration of response (DOR) of the combination of BXCL701 and PEMBRO in Cohort A and B.
- To continue to characterize the safety profile of BXCL701 in combination with PEMBRO.
- To assess the population pharmacokinetics of BXCL701 using sparse pharmacokinetic sampling.
- To assess the pharmacodynamic profile of the combination of BXCL701 and PEMBRO by measuring relevant effects on those cytokines previously shown to be modulated by BXCL701 in humans.

The secondary objective of the Phase 2b study are:

- To estimate the CRR, OS, duration of response, rPFS, and PSA PFS. of the BXCL701 + PEMBRO combination and monotherapy in Cohort A and B, respectively. 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
  - 50% or greater PSA decline from baseline.

Exploratory Objectives (Phase 2a and Phase 2b)

- To evaluate the response rate by Immune Response Evaluation Criteria in Solid Tumors (iRECIST) criteria with BXCL701 in combination with PEMBRO.

- To evaluate the quantitative and qualitative effects of BXCL701 in combination with PEMBRO on relevant immune effector cytokines and various immunological effector cells in blood and, whenever feasible, in tumor tissues.
- To explore the predictive value of baseline programmed death ligand 1 (PD-L1) tumor expression in metastatic tumor tissue with subsequent clinical outcomes.
- To explore the relationship between baseline tumor messenger ribonucleic acid (mRNA) immune profiling panel and clinical outcomes.

Study Design:

This is an open-label, multicenter, Phase 1b/2 study to identify the recommended Phase 2 dose and assess the efficacy and safety of BXCL701 administered orally, as monotherapy and in combination with PEMBRO, in patients with mCRPC. Patients enrolled in the Phase 2a portion of the study will have either SCNC (Cohort A) or adenocarcinoma (Cohort B) phenotype, while the Phase 2b randomized portion of the study will enroll only the histologic subtype(s) showing preliminary evidence in Phase 2a. The study will also assess other efficacy parameters, such as rPFS, PSA PFS, OS, and DOR, as well as the safety of the combined treatment. The study will consist of three components:

- Phase 1b: Safety and tolerability of the combination of BXCL701 administered on Days 1 to 14 of a 21-day cycle plus PEMBRO 200 mg administered intravenously (IV) on Day 1 of every 21 days, will be assessed and confirmed in patients with mCRPC. In the first cohort enrolled in the study, the initial dose level of BXCL701 will be 0.4 mg; if there are no safety concerns, this will be escalated to a total daily dose of 0.6 mg.
- Phase 2a (Simon 2-Stage): Patients will be treated with BXCL701 in combination with PEMBRO. Patients will be grouped in 1 of 2 cohorts based on phenotype.
    - Cohort A: Patients with any small cell or neuroendocrine features, either de novo or treatment-emergent included mixed SCNC.
    - Cohort B: Patients with adenocarcinoma and no evidence of small cell or neuroendocrine features.
- Phase 2b (for the histologic subtype[s] showing preliminary efficacy in Phase 2a): Patients within a given subtype will be randomized 2:1 to receive either BXCL701 combined with PEMBRO or BXCL701 monotherapy. The purpose of the Phase 2b component is to estimate efficacy outcomes in each treatment group individually with the BXCL701 monotherapy arm serving as an internal reference group; the two treatment groups will not be formally compared and crossover from monotherapy to combination treatment is permissible upon radiographic disease progression with monotherapy. In addition, the total experience for patients within the mCRPC histologic subtype from the Phase 2a and Phase 2b components will collectively provide greater precision in relation to the efficacy and safety of the combination regimen.

Phase 1b:

Patients will be observed for dose-limiting toxicity (DLT) during Cycle 1. Three patients will be treated initially with BXCL701 0.4 mg plus PEMBRO:

- If there are no DLTs in Cycle 1, the dose of BXCL701 will be escalated to a total daily dose of 0.6 mg in the next cohort of 3 patients.
- If ≥1 of the 3 original patients has a DLT in Cycle 1, after a discussion between the sponsor and the investigator, either 3 patients (if 1 patient experiences a DLT) or 6 to 9 patients (if 2 or 3 patients experience a DLT) will be added at the 0.4 mg BXCL701 dose level. For this expanded 0.4 mg cohort:
    - If none of the patients experience a DLT, consideration will be given to dose escalation to BXCL701 0.6 mg plus PEMBRO.

- If 1/3 of the patients experience a DLT, the Phase 2 can commence.
- If >1/3 of the patients experience a DLT, a discussion will be held between the investigator and sponsor as to how to proceed.

Following dose escalation to BXCL701 0.6 mg plus PEMBRO in 3 patients:

- If there are no DLTs at this dose level, the Phase 2a enrollment can commence.
- If ≥1/3 patients have a DLT in Cycle 1, after a discussion between the sponsor and the investigator, 6 to 9 patients will be added at the 0.6 mg BXCL701 total daily dose level; and consideration of an alternate dosing (e.g., split dose) schedule may be given.
- For this additional cohort of 6 to 9 patients:
  - If ≤1/3 of the patients experience a DLT, the Phase 2a component can commence.
  - If >1/3 of the patients experience a DLT, consideration will be given to the use of 0.4 mg BXCL701 total daily dose, or an intermediate dose, plus PEMBRO in Phase 2a.

A Safety Review Committee, which will be comprised of both investigators and sponsor representatives, will review the safety during the Phase 1b part of the study and during the trial before the Phase 2a and Phase 2b components begin. If an intermediate dose is selected at the end of Phase 1, the committee will monitor the first 6 Phase 2a patients through Cycle 1.

All safety data from all patients enrolled in each dose cohort will be reviewed to confirm any DLTs that were experienced and to determine enrolling the next cohort, as well as the BXCL701 dosing regimen to be used in the Phase 2 portions. Unless doses were held because of adverse events (AEs), a patient must have received >70% of planned BXCL701 doses in Cycle 1 (e.g., ≥10 of 14 planned doses) with PEMBRO dosed on Day 1 of Cycle 1 to be eligible for DLT assessment.

Phase 1 patients who do not meet the criteria for discontinuation will be allowed to continue treatment. Once the recommended total daily dose for BXCL701 is determined, any patients still tolerating treatment in a lower BXCL701 dose cohort may have their BXCL701 doses escalated to the recommended dosing regimen with the start of the next cycle at the investigator's discretion.

Phase 2a:

After assessment of safety and confirmation of the BXCL701/PEMBRO dose regimen (i.e., either a 0.6 mg, 0.4 mg, or an intermediate total daily dose of BXCL701) to be used in the subsequent stage, the Phase 2a enrollment will begin. Eligible patients will receive BXCL701 on Days 1 to 14 of a 21-day cycle plus PEMBRO 200 mg administered IV on Day 1 of every 21 days.

Phase 2b:

Upon the completion of the Phase 2a and achievement of the protocol required composite responses for a given histologic subtype, the Phase 2b enrollment will begin for that subtype. Eligible patients will be randomized 2:1 to receive either the following, respectively:

- Combination therapy of BXCL701 on Days 1 to 14 of a 21-day cycle plus PEMBRO 200 mg administered IV on Day 1 of every 21 days.
- Monotherapy BXCL701 on Days 1 to 14 of a 21-day cycle. Upon radiographic disease progression with monotherapy, crossover to combination treatment is allowed.

Study Design Features (all phases of the study):

Across all study phases, patients will be screened for study eligibility within 28 days before the first study drug dose after provision of written informed consent. Patients who are determined to be eligible, based on

Screening assessments, will be enrolled in the study on Cycle (C)1, Day (D)1 (baseline, before the first dose of BXCL701).

During treatment, patients will attend study center visits and have study evaluations performed as detailed in the Schedule of Assessments (Table 2). All study visits will be conducted on an outpatient basis but may be conducted on an inpatient basis per the investigator's judgement.

Patients may continue to receive treatment until the development of radiographic progression by RECIST 1.1/Prostate Cancer Working Group 3 (PCWG3) criteria, unequivocal clinical progression, unacceptable toxicity, another discontinuation criterion is met, or closure of the study; no maximum duration of therapy has been set. Patients with PSA progression in the absence of radiographic or clinical progression should continue to receive protocol therapy. Treatment may continue beyond the first radiographic progression if there is clinical benefit.

BXCL701 dose modifications within a treatment cycle are not permitted in Cycle 1 in the absence of a DLT. In Cycle ≥2, dose reduction modifications within a treatment cycle will be at the discretion of the investigator. Doses should be taken at approximately the same time every day. BXCL701 should not be taken on an empty stomach. Doses held because of AEs should not be made up on subsequent days within or following a cycle. A dose that is missed for reasons other than an AE (e.g., the patient forgets to take a dose) may be taken at least 6 hours prior to the next planned dose; otherwise, the missed dose may be administered on a day subsequent to a scheduled dose. Any additional adjustments should be discussed with the medical monitor or designee. If a dose is vomited within approximately 10 minutes of dosing, the patient may be re-dosed. If the patient vomits >10 minutes after dosing, no further attempts at dosing that particular dose should take place; dosing should resume with the next dose. Under no circumstances should missed doses be made-up when the patient is already taking a planned dose (i.e., no "doubling-up" to account for missed doses).

Patients will complete an End of Treatment (EOT) visit prior to crossover (if applicable) and upon discontinuation of the study treatment, within 21 days after their last dose of study drug. Upon discontinuation of study treatment, Safety Follow-Up is to be conducted 30 days (± 7 days) after their last dose of protocol therapy as well as at additional subsequent time points if drug-related AEs have not yet resolved. Patients will also be contacted by telephone approximately every 90 days for clinical evidence of progressive disease (PD) in settings in which discontinuation of study therapy was for reasons other than PD (tumor measurements as specified in the protocol are not required after the EOT visit), and for assessment of survival status. This extended follow-up for disease status and survival after discontinuation of study treatment will continue for up to 12 months after study treatment is discontinued.

Safety will be assessed during the study by documentation of AEs, clinical laboratory tests, physical examination, vital sign measurements, and Eastern Cooperative Oncology Group (ECOG) performance status.

All patients must have pre-treatment (prior to study treatment dosing) imaging (computed tomography [CT] scan of chest/abdomen/pelvis or magnetic resonance imaging [MRI] for baseline tumor measurements, as well as bone scintigraphy [BS]). Patients with skin, subcutaneous, or lymph node metastases may also have tumor evaluations (including measurements, with a ruler) by means of physical examination. Patients with a history of central nervous system (CNS) malignant involvement or CNS symptoms should have either CT or MRI imaging of the brain performed to assess active CNS malignancy.

Tumor measurements and disease response assessments (CT or MRI; BS) are also to be performed at the end of Cycle 3 (approximately 9 weeks after the first study treatment dose), and then approximately every 9 weeks thereafter until development of PD. Patients on monotherapy, with evidence of radiographic progression, may crossover to receive the combination. For patients with evidence of disease control (stable disease or better) at Week 27, tumor measurements and disease response assessments may be performed

less frequently (approximately every 12 weeks) thereafter at the discretion of the investigator. Tumor measurements and disease response assessments also are to be performed at the EOT visit.

Additionally, measurement of serum PSA will be performed on Day 1 of every treatment cycle.

Population pharmacokinetics of BXCL701 will be assessed using sparse pharmacokinetic sampling.

All remaining samples at the end of the study will be de-identified with respect to the patient and moved into long-term storage for up to 5 years for future analysis, after which time the samples will be destroyed.

Patients with PSA-only progression in the absence of radiographic or clinical progression should continue to receive protocol therapy per PCWG3 guidelines.

Number of Patients (Planned):

Approximately 6 to 12 evaluable patients with mCRPC will be enrolled in the Phase 1b component of the study.
Approximately 30 to 56 evaluable patients will be enrolled in the Phase 2a component of the study.
Approximately 60 evaluable patients with a given mCRPC histologic subtype (SCNC or adenocarcinoma) will be enrolled in the Phase 2b component of the study. If both subtypes are evaluated, then the Phase 2b component will enroll approximately 120 patients.

Eligibility Criteria:

All patients must satisfy the following inclusion and exclusion criteria to be eligible for entry into the trial.

Inclusion criteria:

1. Patient has evidence of progressive mCRPC, as defined by PCWG3 criteria.
   a. Patients with de novo small cell prostate cancer are not required to have received androgen deprivation therapy (ADT).
2. Progression during or following completion of at least 1 prior line of systemic therapy for locally advanced or metastatic prostate cancer.
3. Phases 2a and 2b only:
   SCNC – Cohort A of Phase 2a; not applicable to Phase 2b:
   a. Patient has histologic evidence of SCNC either with archival tissue or a fresh tumor biopsy obtained during Screening. Archival or fresh tumor biopsy tissue must be submitted for a central laboratory pathology review; however, enrollment can proceed if SCNC is determined by a local pathology review.
   b. Patient has previously received at least 1 prior line of cytotoxic chemotherapy. Patients who either have refused chemotherapy or are considered unsuitable for chemotherapy may be eligible following discussion with the sponsor.
   c. Must be willing to undergo metastatic tumor biopsy during Screening. Requirement may be waived in patients without a safely accessible lesion or for patients with evaluable archival metastatic tumor tissue.
   d. Has measurable disease per RECIST 1.1 criteria.

   Adenocarcinoma - Cohort B of Phase 2a; randomized population for Phase 2b:

   a. Patient has histologically or cytologically confirmed adenocarcinoma of the prostate without small cell neuroendocrine features.
   b. Patients with soft tissue disease must provide a fresh core or excisional biopsy or archival tissue from a site not previously irradiated for central pathology review; however, enrollment may proceed if predominant adenocarcinoma without small cell neuroendocrine features is determined by local pathology review.

c. Has been treated with at least 1 but no more than 2 second generation AR pathway target agents (e.g., abiraterone acetate and/or enzalutamide or other next generation agent) and at least 1 regimen/line of taxane containing chemotherapy in the metastatic castration-sensitive prostate cancer (mCSPC) or mCRPC setting. Patients with known actionable mutations should have progressed on applicable standard care targeted therapy or have documented intolerance to or be unsuitable for such therapy.
d. RECIST 1.1 measurable disease or detectable bone metastases by whole body bone scintigraphy.

4. Patient has serum testosterone <50 ng/dL during Screening except for those with de novo small cell prostate cancer.
   a. Patients with treatment-emergent SCNC without a history of bilateral orchiectomy are required to remain on luteinizing hormone-releasing hormone (LHRH) analog during the course of protocol therapy except for patients with de novo small cell prostate cancer.
5. Patient has an ECOG performance status of 0-2.
6. Patient is ≥18 years of age.
7. Patient's acute toxic effects of previous anticancer therapy have resolved to ≤ Grade 1 except for Grade 2-3 peripheral neuropathy or any grade of alopecia.
8. Patient has adequate baseline organ function, as demonstrated by the following:
   a. Serum creatinine (Cr) ≤1.5 times institutional upper limit of normal (ULN) or calculated Cr clearance >50 mL/min.
   b. Serum albumin ≥2.5 g/dL.
   c. Total bilirubin ≤1.5 × ULN.
   d. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × institutional ULN (patients with hepatic metastases must have AST/ALT ≤5 × ULN).
9. Patient has adequate baseline hematologic function, as demonstrated by the following:
   a. Absolute neutrophil count (ANC) ≥1.5 × 10^9/L;
   b. Hemoglobin ≥8 g/dL and no red blood cell transfusions during the prior 14 days;
   c. Platelet count ≥100 × 10^9/L and no platelet transfusions during the prior 14 days.
10. Male patients and their female partners of childbearing potential must agree and commit to use a barrier contraception (e.g., condom with spermicide throughout the duration of the study until at least 6 months following the last dose of study drug, in addition to their female partners using either an intrauterine device or hormonal contraception and continuing until at least 6 months following the last dose of study drug. This criterion may be waived for male patients who have had a vasectomy >6 months before signing the informed consent form. [Note: In the United States, female partners of study participants are not required to use contraception as a condition of their partner's eligibility, but female partners with childbearing potential should consider use of effective methods of contraception for the duration of their male partner's study participation and for at least 6 months following the last dose of study medication.
11. Patient has signed informed consent prior to initiation of any study-specific procedures or treatment.
12. Patient is able to adhere to the study visit schedule and other protocol requirements, including follow-up for OS.

Exclusion criteria:

1. Patient has received treatment with >2 cytotoxic chemotherapy regimens for castration-resistant prostate cancer (CRPC). Chemotherapy in the hormone-sensitive setting does not count in this

assessment provided the last dose was >6 months before study entry. A change in chemotherapy agents due to intolerance after brief exposure may not count in this assessment, pending review with Medical Monitor.

2. Patient has received external-beam radiation or another systemic anticancer therapy within 14 days or 5 half-lives, whichever is shorter, prior to study treatment.
3. Patient has received treatment with an investigational systemic anticancer agent within 14 days prior to study drug administration.
4. Patient has received 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 (e.g., cytotoxic T lymphocyte–associated antigen 4 [CTLA-4], OX-40, CD137), or requires concomitant treatment with DPP4 inhibitors (e.g., gliptins).
5. Patient has an additional active malignancy that may confound the assessment of the study endpoints. If the patient has a past cancer history (active malignancy within 2 years prior to study entry) with substantial potential for recurrence, this must be discussed with the sponsor before study entry. Patients with the following concomitant neoplastic diagnoses are eligible: non-melanoma skin cancer and carcinomas in situ (including transitional cell carcinoma, anal carcinoma, and melanoma in situ).
6. Patient has clinically significant cardiovascular disease (e.g., uncontrolled or any New York Heart Association Class 3 or 4 congestive heart failure, uncontrolled angina, history of myocardial infarction, unstable angina or stroke within 6 months prior to study entry, uncontrolled hypertension, or clinically significant arrhythmias not controlled by medication).
7. Patient has QT interval corrected for heart rate using Bazett's formula (QTcB) >480 msec at Screening.
8. Patient has uncontrolled, clinically significant pulmonary disease (e.g., chronic obstructive pulmonary disease, pulmonary hypertension) that in the opinion of the investigator would put the patient at significant risk for pulmonary complications during the study.
9. Patient has brain or leptomeningeal metastases that are symptomatic and progressive on imaging. Patients with a history of CNS metastases must have received appropriate treatment. Central nervous system imaging is not required prior to study entry unless there is a history of CNS involvement or clinical suspicion of CNS involvement. Imaging of patients with a prior history of CNS metastases should be compared to prior imaging to discern PD.
10. Patient has an active autoimmune disease or Grade ≥3 (non-infectious) pneumonitis that has required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) or treatment with drugs (e.g., neomercazol, carbimazole) that function to decrease the generation of thyroid hormone by a hyperfunctioning thyroid gland (e.g., in Graves' disease) is not considered a form of systemic treatment of an autoimmune disease.
11. Patient has a diagnosis of immunodeficiency or is receiving systemic steroid therapy at a prednisone equivalent dose of >10 mg daily for at least 1 week or other form of immunosuppressive therapy within 7 days prior to Cycle 1 Day 1 (C1D1).
12. Patient has uncontrolled intercurrent illness including, but not limited to, uncontrolled infection, suspected or active Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection,

disseminated intravascular coagulation, or psychiatric illness/social situations that would limit compliance with study requirements.

13. Patient has known positive status for human immunodeficiency virus, active or chronic Hepatitis B, or Hepatitis C. Screening is not required.
14. Patient has any medical condition that, in the opinion of the investigator, places the patient at an unacceptably high risk for toxicity.
15. Any dysphagia, odynophagia, esophageal dysmotility or stricture, known GI malabsorption syndrome, or intractable diarrhea that may significantly alter the absorption of orally administered study drug.
16. Patients with history of symptomatic orthostatic hypotension within 3 months prior to enrollment. Orthostatic hypotension is defined as a drop in systolic blood pressure (BP) of ≥20 mmHg or diastolic BP of ≥10 mmHg with assumption of an upright posture.

Investigational Product, Dosage, and Mode of Administration

BXCL701:

BXCL701 tablets contain valine-proline boronic acid formulated as the methanesulfonate salt. Current dosage strengths include 0.05-mg and 0.1-mg tablets for oral administration.

The starting dose regimen of BXCL701 (i.e., the dose regimen in Cohort 1 of the Phase 1b) is 0.4 mg once daily (QD) on Days 1-14 every 21 days. BXCL701 should not be taken on an empty stomach. The BXCL701 dose regimen for any patient depends on the Phase 1 dose cohort in which the patient is enrolled. Additional dosing schedules may also be evaluated as part of the Phase 1 dose and schedule evaluation.

To minimize risk of hypotension, patients should be advised to maintain adequate hydration while on-treatment, such as drinking at least 2 liters of fluids per day, including fluids with electrolytes. Factors such as strenuous exercise, heat, humidity, fever, gastrointestinal disturbance may increase hydration needs. Administration of at least 1 liter of intravenous (IV) fluids is required at Cycle 1 Day 1.

On days when pharmacodynamic studies are being performed, BXCL701 should be administered at the study center and should be administered at (approximately) the same times of day on each treatment day in the cycle. In cycles in which pharmacodynamics are not evaluated, BXCL701 also should be administered at (approximately) the same times of day on each treatment day in the cycle.

Pembrolizumab (PEMBRO):

The PEMBRO dose will be 200 mg, administered as an IV infusion over 30 minutes (±5 minutes) on Day 1 of each 21-day cycle.

Assessments

Assessments for safety, efficacy, and biological/correlative effects will be performed according to the schedules outlined in the Schedule of Assessments.

Safety assessments:

Safety assessments include DLTs, AEs, serious adverse events (SAEs), physical examinations, vital sign measurements, clinical laboratory evaluations, and reasons for treatment discontinuation due to toxicity.

The AE reporting period begins with the initiation of study treatment and continues through 30 days after the last dose of protocol therapy. All AEs that occur in treated patients during the AE reporting period specified in the protocol must be reported to the sponsor, whether or not the event is considered related to

BXCL701 or PEMBRO. Any known untoward event that occurs beyond the AE reporting period that the investigator assesses as related to BXCL701 or PEMBRO should also be reported as an AE.

Serious AEs occurring after the patient has provided informed consent, but before the first dose of study treatment, will be collected as medical history unless the event is either new and attributed to protocol-mandated procedures by the Investigator, or there is a significant change in the rate of occurrence or an increase in the severity of the pre-existing condition which is judged to be clinically important and attributed to the protocol-mandated procedures by the Investigator. Any SAE or death occurring during the treatment period and/or within 30 days following the last dose of study medication must be reported to IQVIA Biotech within 24 hours of first knowledge of the occurrence. The site should submit an SAE form within 24 hours to IQVIA Biotech Safety. If any SAE occurs, study treatment should be interrupted or discontinued at the discretion of the physician investigator.

Efficacy assessments:

Tumor lesion size will be assessed radiographically at Cycle 4 Day 1, and every third successive cycle. A responder will be any patient who achieves an objective response as defined by RECIST 1.1 guidelines.

PSA will be assessed at every cycle. A responder will be considered any patient whose PSA decreases from baseline by 50% or more.

Phase 2a: Efficacy endpoints include the following:

- Composite response rate
    - Objective response as defined by RECIST 1.1 guidelines
    - Decrease in PSA from baseline ≥50%
    - CTC conversion from ≥5/7.5 mL to <5/7.5 mL per Veridex assay
- Radiographic progression-free survival (rPFS)
- Prostate serum antigen (PSA) PFS
- Overall survival (OS)

Duration of response (DOR)

Phase 2b: Efficacy endpoints include the following:

- Objective response as defined by RECIST 1.1 guidelines.
- 50% or greater decrease in PSA from baseline.
- rPFS.
- PSA PFS.
- OS.
- DOR.

Determination of Sample Size:

Approximately 6 to 12 patients with mCRPC will be enrolled in the Phase 1b component of the study.

For each cohort in the Phase 2a component, approximately 15 to 28 patients will be enrolled, and a Simon's 2-stage minimax design will be used. The null hypothesis that the true composite response rate is <15% will be tested against the alternative that the true composite response rate is ≥35% (one-sided type 1 error = 0.046, power = 80%). In each cohort, 15 patients will be accrued in the first stage. If there are 2 or fewer composite responses in these 15 patients, accrual to the cohort will be halted. Otherwise, 13 additional patients will be accrued in the second stage, for a total of 28 patients per cohort. The null hypothesis will be rejected if 8 or more composite responses are observed in 28 patients.

For a given histologic subtype (SCNC or adenocarcinoma), the Phase 2b component will randomize a total of 60 patients, 2:1 to receive the Phase 2a combination regimen of BXCL701 + PEMBRO (n = 40) vs. BXCL701 monotherapy (n = 20). The purpose of the Phase 2b component is to estimate efficacy outcomes in each treatment group individually, with the BXCL701 monotherapy arm serving as an internal reference group; the two treatment groups will not be formally compared. A response rate of 25-35% in 40 patients treated with BXCL701 + PEMBRO will result in a 31% absolute maximum width of the estimated exact 95% confidence interval (CI). A response rate of 5-15% in 20 patients treated with BXCL701 monotherapy arm will result in a 35% absolute maximum width of the estimated exact 95% CI. If the observed e response rate is 10/40 (25%) in patients treated with BXCL701 + PEMBRO and 2/20 (10%) in patients treated with BXCL701 monotherapy, then the two-sided 80% confidence interval for the difference in response rates (Miettinen and Nurminen, 1985) would be (0.96 - 26.8), ruling out 0.

In addition, the total experience for patients within the mCRPC histologic subtype from the Phase 2a and Phase 2b components will collectively provide greater precision the efficacy and safety of the combination regimen. A pooled (non-comparative) analysis of the Phase 2a (n = 28) and Phase 2b patients (n = 40) with a given histologic subtype receiving the combination regimen will provide the following precision in the estimation of the composite response rates (n = 68 total). The lower bound of the confidence interval will inform whether the pooled response rate is clinically meaningful. Based on an expected 5-10% response rate among mCRPC patients who receive PEMBRO monotherapy (Antonrakis, 2019), the table below suggests that observing 13 responses (19.1%) will be clinically meaningful, as it will rule out a <10% response rate with 95% confidence.

Response rate BXCL701 + PEMBRO (n = 68)	**95% confidence interval[a]**
13/68 (19.1%)	(10.5% - 30.5%)
17/68 (25.0%)	(15.3% - 37.0%)
21/68 (30.9%)	(20.2% - 43.3%)
[a]Clopper-Pearson exact method	

Statistical Methods:

Safety:

Demographic (e.g., gender, age, race) and baseline characteristics (e.g., ECOG performance status, height, weight, and prior therapy) will be summarized by BXCL701 dose group and disease cohort using descriptive statistics. Treatment-emergent AEs through 30 days after last dose of study treatment will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) Version 13.1 (or higher) System Organ Class and Preferred Term. The incidences and percentages of patients experiencing each AE preferred term will be summarized with descriptive statistics. Adverse events will also be summarized by

the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03 (or higher) grade, and by causality (attribution to study treatment). Dose-limiting toxicities, Grade 3 to 4 AEs, SAEs, and AEs resulting in dose modification or treatment discontinuation will be summarized by preferred terms.

Laboratory results will be classified according to NCI CTCAE, Version 4.03 (or higher). Laboratory results not corresponding to an NCI CTCAE term will not be graded. Incidences of laboratory abnormalities will be summarized with descriptive statistics.

Vital signs and physical examination results will be summarized with descriptive statistics.

Safety outcomes will be summarized separately for the Phase 1b component (by dose cohort), Phase 2a (by disease cohort), and Phase 2b histologic subtype (by treatment arm). In addition, safety data will be combined across all patients from who receive at least one dose of the combination regimen of BXCL701 + PEMBRO.

Efficacy:

Composite response rate in the Phase 2a is defined as the proportion of patients achieving 1 or more of the following: 1) objective response by RECIST 1.1 criteria, 2) ≥50% decline from baseline in serum PSA, or 3) CTC conversion from ≥5/7.5 mL to <5/7.5 mL per Veridex assay. The DOR is defined as the time from the date measurement criteria are first met for partial response (PR)/complete response (CR) to the date measurement criteria are first met for PD or death from any cause, whichever occurs first. Radiographic PFS is defined as the time from the date of initiation of protocol therapy to the date measurement criteria are first met for PD by RECIST 1.1/PCWG3 criteria or death from any cause, whichever occurs first. The PSA PFS is defined as the time from the date of initiation of protocol therapy to the date measurement criteria are first met for PSA progression by PCWG3 criteria or death from any cause, whichever occurs first. The OS is defined as the time from the date of initiation of protocol therapy to the date of death from any cause. Distributions for rPFS, PSA PFS, DOR, and OS will be estimated by Kaplan Meier methodology.

References:

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BIOXCEL THERAPEUTICS PROTOCOL BXCL701-201

A PHASE 1B/2 STUDY OF BXCL701, A SMALL MOLECULE INHIBITOR OF DIPEPTIDYL PEPTIDASES (DPP), ADMINISTERED IN COMBINATION WITH THE ANTI-PROGRAMMED CELL DEATH 1 (PD1) MONOCLONAL ANTIBODY PEMBROLIZUMAB (PEMBRO; KEYTRUDA®) IN PATIENTS WITH MCRPC EITHER SMALL CELL NEUROENDOCRINE PROSTATE CANCER (SCNC, NEPC) OR ADENOCARCINOMA PHENOTYPE

1. INTRODUCTION

Prostate cancer is the most common malignancy in men and the second leading cause of cancer-related deaths. [1] In 2021 it is estimated that there will be approximately 248,530 new cases of prostate cancer and 34,130 deaths from prostate cancer in the US.[2] Prostate cancer develops mainly in older men and in African American men. The average age at the time of diagnosis is approximately 66 years, with approximately 60% of cases diagnosed in men ages 65 years or older. It is rare in men <40 years of age.

Most prostate cancers are classified as adenocarcinomas, characterized by absence of basal cells and uncontrolled proliferation of malignant tumor cells with luminal cell features including glandular formation and expression of androgen receptor (AR) and PSA. A number of systemic treatment options are available for patients with mCRPC- with predominant adenocarcinoma phenotype. Recently, the second-generation targeted endocrine therapies, enzalutamide and abiraterone, were each found to have superior OS versus control (placebo and prednisone, respectively) in patients with mCRPC before treatment with chemotherapy. [3, 4] A docetaxel containing regimen is currently the chemotherapy of choice after disease progression with second generation hormonal therapies based on an improvement in median overall survival of 18.9 months versus 16.5 months for mitoxantrone in a randomized trial.[5] Cabazitaxel, a second taxane, was also associated with superior survival in patients after docetaxel – median 15.1 months versus 12.7 months with mitoxantrone,[6] but has had limited use because of its toxicity profile. Data continues to emerge for small subsets of patients with actionable mutations, such as rucaparib, a PARP inhibitor recently approved for the patients with BRCA mutations after chemotherapy, [7] but the majority of patients do not have mutations associated with therapeutic options. Therefore, an unmet medical need remains for patients in the mCRPC setting with adenocarcinoma phenotype after treatment with targeted hormonal therapy and docetaxel.

Small cell neuroendocrine prostate cancer (SCNC; NEPC) is composed of predominantly neuroendocrine tumor cells that are highly proliferative and aggressive, causing death in months; these cells do not express AR or PSA. It has been observed that SCNC occurs de novo or as a recurrent tumor in patients who have received hormonal therapy for prostatic adenocarcinoma.[8,9] Such tumors do not respond to hormonal therapy targeting the AR signaling pathway, and so accurate diagnosis of SCNC is important.[10] Treatment of SCNC typically requires early combination chemotherapy and locoregional control of bulky tumor deposits, including untreated or recurrent primaries.[11]

The treatment-emergent form of SCNC (-tSCNC-) has recently been characterized.[12] Patients with progressive metastatic castration-resistant prostate cancer (mCRPC) underwent metastatic tumor biopsy and were followed for survival. It was observed that tSCNC was present in 17% of patients with mCRPC and was associated with shortened survival. Genomic alterations in the DNA repair pathway were nearly mutually exclusive with t-SCNC differentiation (p=0.035), suggesting t-SCNC may be a distinct subset of mCRPC-. Transcriptional profiling could help in the identification of novel therapeutic targets for SCNC.

Pembrolizumab is a humanized monoclonal antibody (mAb) of the IgGr/kappa isotope designed to directly block the interaction between the programmed cell death-1 (PD-1) receptor and its ligands, PD-L1 and PD-L2. Pembrolizumab is approved in the US, EU, and other countries for several malignancies and settings within malignancies, with additional global development ongoing in a broad range of clinical trials in a variety of additional tumor types, including mCRPC. In KEYNOTE 199, single-agent treatment with pembrolizumab in patients following ≥1 second generation hormonal therapy and 1 or 2 regimens of chemotherapy, including docetaxel resulted in RECIST 1.1 ORR of 5% for PD-L1 positive disease and 3% for PD-L1 negative disease.[13] Confirmed PSA response was 8%, 5% and 1% for PD-L1 positive, PD-L1 negative and Bone predominant disease respectively. Subsequent clinical studies of pembrolizumab in patients with mCRPC focus on combination regimens with established treatments.

BXCL701 (also known as talabostat and valine-proline boronic acid) is an orally administered, small molecule inhibitor of dipeptidyl peptidase (DPP) such as DPP8 and 9. This study is being conducted to evaluate the antitumor activity of BXCL701 in patients with mCRPC, both SCNC and adenocarcinoma phenotype.

1.1. BXCL701 Mechanism of Action

BXCL701 is a competitive inhibitor of DPPs, including DPP4 (CD26), DPP8, and DPP9, members of the post-prolyl-cleaving protease family. By inhibiting DPP8 and DPP9, BXCL701 treatment results in robust immunostimulation via several mechanisms. One such mechanism is by inhibiting DPP8 and DPP9 in macrophages in the tumor microenvironment and lymph nodes, which, in turn, release interleukin (IL)-1β, a potent activator of immune effector cells that release numerous other cytokines and chemokines that contribute to anti-tumor activity.

BXCL701 has also been shown to inhibit FAP, which has previously been described as a type II membrane protein with DPP and gelatinase activity. Studies of FAP have reported that FAP expression is induced in fibroblasts associated with the stroma of malignant epithelial tumors. These reports suggest that FAP does not appear to be expressed constitutively in most healthy tissues of the adult animal; however, experiments have demonstrated the expression of FAP in bone marrow and lymphoid tissue from both healthy and tumor-bearing mice. Fibroblast activation protein, as well as DPP8 and 9, are expressed and activated in a wide range of malignancies, especially mCRPC, that emerge following treatment of mCRPC with second generation anti-androgen (enzalutamide) or cytochrome P450 (CYP)17 (abiraterone) inhibitors. Resistance to androgen ablation therapy also results in the expression of PDL1, and there is robust correlation between the

expression of PDL1 and the targets of BXCL701, particularly FAP, DPP8, and DPP9. In animal models with fully intact immune systems, BXCL701 and PD-1 inhibitors resulted in synergistic anticancer activity.

1.2. Preclinical Pharmacology

In a purified enzyme system, BXCL701 inhibits DPP4/CD26 and FAP activity with half maximal inhibitory concentration (IC_{50}) values of 1.0 and 32.0 nM, respectively, while inhibiting DPP8 and DPP9 with IC_{50} values of 2.7 and 3.2 nM, respectively. Dipeptidyl peptidase 4/CD26 is a serine protease expressed on a variety of tissues, including T lymphocytes, endothelial cells, and epithelial cells, and has been shown to play an important role in tumor progression. It has been found to be expressed in non-small cell lung cancer (NSCLC), chronic lymphocytic leukemia (CLL), lymphoma, and melanoma. In 1 series, 93% of all cases of lung adenocarcinomas were positive for aberrant- DPP4/CD26 activity.[14]

Fibroblast activation protein is a type II integral membrane glycoprotein belonging to the serine protease family. It is a 95-kD cell surface glycoprotein expressed by tumor stromal fibroblasts and well expressed by reactive stromal fibroblasts in more than 90% of human epithelial carcinomas (breast, lung, colorectal, ovary) as determined by immunohistochemistry. In an evaluation of a series of malignant tumors, FAP was expressed in the stroma of all 13 lung tumor samples that were examined. Neural and lymphoid cells, as well as surrounding normal tissue, do not express FAP. Fibroblast activation protein expression in normal tissue has only been observed in a subset of pancreatic endocrine cells, bone marrow stromal cells, and transiently in healing wounds. Epithelial carcinoma cells are also FAP-negative, making FAP an attractive target for the study of tumor stromal cell biology. Stromal cells residing in colorectal adenomas are also predominantly FAP-negative, suggesting that malignancy is required for effective FAP induction. Some bone and soft-tissue sarcomas are also known to express FAP, consistent with FAP's mesenchymal origin. Thus, FAP is selectively expressed by tumor stromal fibroblasts in epithelial carcinomas, but not by epithelial carcinoma cells or normal fibroblasts.[14.]

Dipeptidyl peptidases 8 and 9 are expressed widely in a number of tissues, but notably in monocytes and macrophages, where their inhibition with BXCL701 has been compared to the action of an immune checkpoint inhibitor through the activation of an immunogenic cell death called pyroptosis.[15] Current checkpoint inhibitor- based therapies largely target T-cells, members of the adaptive immune system, while monocytes and macrophages belong to the innate immune system. Thus, it is an attractive approach to target the cells of the innate immune system, using BXCL701 as a single agent, or even more compelling to use BXCL701 in combination with checkpoint inhibitors targeting the adaptive immune system.

In syngeneic mouse models utilizing the WEHI 164 fibrosarcoma cell line, BXCL701 significantly inhibited tumor growth, both as a single agent and in combination with chemotherapies. BXCL701 also significantly inhibited the growth of a human osteosarcoma, SK-ES-01, in mouse xenografts.[14] A study conducted in a mouse model of metastases using a sarcoma cell line at the National Cancer Institute showed that BXCL701

substantially reduced the number of lung metastases in mice.[16] The sponsor has further demonstrated potent activity of BXCL701 in combination with other immune modulating agents including adaptive immune cell checkpoint inhibitors (e.g., anti–PD-1) in several other models. Notably, in these animal models, tumor response was complete and durable, resulting in the generation of a functional memory T-cell response. This is the case because challenge with the same cancer cells resulted in the failure of a subsequent tumor to form in animals that had generated a durable response.

Thus, preclinical data from the literature and generated by the sponsor support the use of BXCL701 as a multimodal DPP inhibitor targeting distinct, yet complementary, mechanisms in the biology of a cancer.

1.3. Clinical Experience

To date, BXCL701 has been administered to more than 700 individuals, including 585 cancer patients in Phase 1, 2, and 3 clinical trials. It was generally well tolerated, and edema and fatigue were the most common AEs seen in these trials.

1.3.1. Healthy Volunteers

Two placebo-controlled Phase 1 studies were conducted in 120 healthy male volunteers (out of whom 90 received BXCL701). BXCL701 was well tolerated at single daily doses up to 2.4 mg and when administered as a single daily dose for 7 days at doses up to 1.8 mg. In the single-dose tolerance study, the most frequently occurring AEs in BXCL701-treated subjects were sensation of temperature change (12/54, 22.2%), tachycardia (11/54, 20.4%), dizziness (8/54, 14.8%) versus 11.1%, 0%, and 0%, respectively, in the placebo group. There were no serious adverse events (SAEs). In the multiple-dose tolerance study, the most frequently occurring adverse events (AEs) in BXCL701-treated subjects were headache (18/36, 50.0%); temperature change sensation (13/36, 36.1%); myalgia (8/36, 22.2%); nausea (6/36, 16.7%); vomiting (5/36, 13.9%); peripheral swelling (5/36, 13.9%); and sore throat (4/36, 11.1%) versus 41.7%, 0%, 16.7%, 0%, 8.3%, 8.3%, and 0, respectively, in the placebo group.

In both studies, BXCL701 significantly increased plasma IL-6 and inhibited plasma DPP4 activity at single doses ≥1.2 mg. Plasma levels of BXCL701 in the multiple dose study suggest a multi-compartmental distribution. The initial distribution Phase was approximately 12 hours. Maximum plasma concentration (C_{max}) appeared to be dose proportional. Time to C_{max} ranged from 1 to 2 hours post-dose. The plasma half-life was not calculated due to a prolonged elimination Phase extending past Day 7. It is thought that BXCL701 binds irreversibly to plasma proteins and that this binding is responsible for the long half-life.

1.3.2. Phase 1 Studies in Patients

BXCL701 was evaluated in two Phase 1 studies: in combination with myelosuppressive chemotherapy in 34 patients with chemotherapy-induced neutropenia at doses up to 1.2 mg/day and in combination with rituximab in 20 patients with B-cell malignancies (non-Hodgkin's lymphoma [NHL] or CLL) at doses up to 0.8 mg/day.

Overall, BXCL701 was well tolerated in both the studies. Edema was the most common AE in both studies (45% and 41%). Other AEs when BXCL701 was administered in combination with myelosuppressive chemotherapy included hypotension (including orthostatic) 10/34 (29%) versus 4/41 (10%); anorexia 5/34 (15%) versus 2/41 (5%); and hypovolemia 4/34 (12%) versus 0. In the B-cell malignancy study with BXCL701 administered in combination with rituximab, other AEs included nausea and fatigue (each in 9 patients, 45%); dizziness (8 patients, 40%); constipation and vomiting (each in 6 patients, 30%); and pyrexia, rigors, and thrombocytopenia (each in 5 patients, 25%).

Efficacy results revealed a relatively consistent 1-day reduction in the total number of days of Grade 4 neutropenia at doses from 0.2 to 0.8 mg, whereas no consistent changes in the median or mean number of days of Grade 3 neutropenia were observed. In the B-cell malignancy study, 2/20 (10%) patients were considered to have a partial response (PR).

1.3.3. Phase 2 Studies

BXCL701 was evaluated in 6 Phase 2 studies: 54 patients in combination with rituximab in advanced CLL at daily doses of 0.6 mg, as a single agent in 42 patients with metastatic melanoma at doses up to 0.8 mg/day, 55 patients with NSCLC in combination with docetaxel at doses up to 0.6 mg/day, 74 patients with metastatic melanoma in combination with cisplatin at doses up to 0.8 mg/day, 68 patients with pancreatic adenocarcinoma in combination with gemcitabine at doses up to 0.6 mg/day, and in 28 patients with metastatic colorectal cancer at doses up to 0.8 mg/day.

Edema, fatigue, nausea, dizziness, and fever were the most common AEs seen these 6 Phase 2 studies. Most of these AEs were either Grade 1 or 2 in nature. Most common Grade 3/4 AEs included dyspnea, neutropenia, fatigue, and hypotension. None of the deaths in any of these studies were attributed to BXCL701.

Antitumor activity was shown by an objective response of PR in 7/54 patients in advanced CLL patients. Two objective responses (1 complete response [CR] and 1 PR) were reported in 33 evaluable patients, for a response rate of 6.1% (2/33) in advanced melanoma. The response rate was 9.1% (5/55) in advanced NSCLC patients in combination with docetaxel. The response rate was 8.1% (6/74) in advanced melanoma patients in combination with cisplatin and 5.9% in advanced pancreatic cancer patients.

1.3.4. Phase 3 Studies

Two Phase 3 studies were conducted with BXCL701, both in advanced NSCLC patients, in combination with docetaxel and pemetrexed, respectively. In both these studies, BXCL701 0.2-mg tablets were administered orally twice daily (BID).

Similar to the AE profile seen in Phase 1 and 2 studies, edema and fatigue were the most common AEs seen in these two Phase 3 studies and were Grade 1 or 2 in nature. Thrombocytopenia and febrile neutropenia were the most common SAEs seen. A few cases of cardiac tamponade were also seen in both the trials. In the study with docetaxel, there was a significant difference with respect to efficacy between the 2 treatment groups in favor of placebo. In the study with pemetrexed, there was no significant difference in the 2 treatment arms with respect to efficacy. No deaths were attributed to BXCL701 during these trials.

1.3.5. Clinical Pharmacokinetics

BXCL701 has negligible protein binding in vitro. It is not metabolized to any appreciable extent and does not inhibit any of the pharmacologically relevant CYP enzymes tested in standard in vitro models. In humans, C_{max} of BXCL701 is achieved approximately 1 to 1.5 hours after oral dosing. The C_{max} and area under the plasma concentration time curve (AUC) tends to increase proportionally with increasing dose. Coadministration of BXCL701 with a high-fat meal resulted in approximately a 30% decrease in mean plasma levels (C_{max}), but no effect on AUC. BXCL701 should not be taken on an empty stomach.

2. STUDY OBJECTIVES

The purpose of the study is to assess the safety and efficacy of BXCL701 monotherapy and in combination with PEMBRO in patients with mCRPC, either SCNC or Adenocarcinoma Phenotype.

In the Phase 1b portion, increasing dose levels of BXCL701 will be explored sequentially in patients with mCRPC regardless of histology.

In the Phase 2a portion of the study, patients will be grouped in 1 of 2 cohorts based on histopathology:

- Cohort A: Patients with any SCNC histopathological features, either de novo or treatment-emergent including mixed SCNC.
- Cohort B: Patients with adenocarcinoma and no evidence of small cell or neuroendocrine features on recent histopathology.

In either cohort, crossover to combination treatment is permissible upon radiographic disease progression in the monotherapy arm.

The objectives below will apply to the Phase 2a and 2b portions of the study and will be assessed with descriptive analyses. Because of the more aggressive nature of the disease for patients in Cohort A (SCNC), the primary and secondary efficacy objectives will be assessed separately by histologic subtype.

2.1. Primary Objectives

Phase 2a primary objectives

- To estimate the composite response rates (CRR) of the combination of BXCL701 + PEMBRO in Cohort A and B, respectively. CRR 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
  - 50% or greater PSA decline from baseline.

Phase 2b primary objective

- To evaluate the response rates defined by RECIST 1.1 criteria, in Cohort A and in Cohort B patients treated with BXCL701 monotherapy and with the combination of BXCL701 + PEMBRO.

2.2. Secondary Objectives

The secondary objectives of the Phase 2a study are:

- To estimate the median radiographic progression-free survival (rPFS) of the combination of BXCL701 and PEMBRO in Cohort A and B.
- To estimate the median PSA progression-free survival (PSA PFS) of the combination of BXCL701 and PEMBRO in Cohort A and B.
- To estimate the median overall survival (OS) of the combination of BXCL701 and PEMBRO in Cohort A and B.
- To estimate the median duration of response (DOR) of the combination of BXCL701 and PEMBRO in Cohort A and B.
- To continue to characterize the safety profile of BXCL701 in combination with PEMBRO.
- To assess the population pharmacokinetics of BXCL701 using sparse pharmacokinetic sampling.
- To assess the pharmacodynamic profile of the combination of BXCL701 and PEMBRO by measuring relevant effects on those cytokines previously shown to be modulated by BXCL701 in humans.

The secondary objective of the Phase 2b study are:

- To estimate the CRR, OS, duration of response, rPFS, and PSA PFS of the BXCL701 + PEMBRO combination and monotherapy in Cohort A and B, respectively. 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
    - 50% or greater PSA decline from baseline.

2.3. Exploratory Objectives

(Phase 2a and Phase 2b)

- To determine the response rate by Immune Response Evaluation Criteria in Solid Tumors (iRECIST) criteria with BXCL701 in combination with PEMBRO.
- To evaluate the quantitative and qualitative effects of BXCL701 in combination with PEMBRO on relevant immune effector cytokines and various immunological effector cells in blood and, whenever feasible, in tumor tissues.
- To explore the predictive value of baseline programmed death ligand 1 (PD-L1) tumor expression in metastatic tumor tissue with subsequent clinical outcomes.
- To explore the relationship between baseline tumor messenger ribonucleic acid (mRNA) immune profiling panel and clinical outcomes.

3. STUDY DESIGN

This is an open-label, multicenter, Phase 1b/2 study to determine the composite response rate of BXCL701 administered orally and daily, combined with PEMBRO, in patients with mCRPC enrolled in Phase 2 with either SCNC (Cohort A) or adenocarcinoma phenotype (Cohort B). The study will also assess other efficacy parameters, such as rPFS, PSA PFS, OS, and DOR, as well as the safety of the combined treatment. The study will consist of 2 Phases:

Phase1b, in which the safety and tolerability of the combination of BXCL701 administered on Days 1 to 14 of a 21-day cycle plus PEMBRO 200 mg administered intravenously (IV) on Day 1 of every 21 days will be assessed and confirmed in patients with mCRPC. In Cohort 1, the initial total daily dose level of BXCL701 will be 0.4 mg; if there are no safety concerns, this will be escalated to a 0.6 mg total daily dose. There will be a 7-day rest period following the last dose of BXCL701 and Day 1 of the subsequent cycle.

Phase 2a (Simon 2-Stage), in which patients will be treated with BXCL701 combined with PEMBRO. Patients will be assigned to 1 of 2 cohorts based on phenotype.

- Cohort A: Patients with any Small Cell/Neuroendocrine features, either de novo or treatment-emergent included mixed SCNC.
- Cohort B: Patients with adenocarcinoma and no evidence of small cell or neuroendocrine features

Phase 2b, in which patients will be randomized 2:1 and treated either with BXCL701 combined with PEMBRO or BXCL701 monotherapy.

- Cohort A: Patients with any Small Cell/Neuroendocrine features, either de novo or treatment-emergent included mixed SCNC.
- Cohort B: Patients with adenocarcinoma and no evidence of small cell or neuroendocrine features.

The purpose of the Phase 2b component is to estimate efficacy outcomes in each treatment group individually with the BXCL701 monotherapy arm serving as an internal reference group; the two treatment groups will not be formally compared. and crossover from monotherapy to combination treatment is permissible upon radiographic disease progression to monotherapy. In addition, the total experience for patients within the mCRPC histologic subtype from the Phase 2a and Phase 2b components will collectively provide greater precision in relation to the efficacy and safety of the combination regimen.

During the Phase 1b, patients will be observed for dose-limiting toxicity (DLT) during Cycle 1. Three patients will be treated initially with 0.4 mg BXCL701 plus PEMBRO:

- If there are no DLTs in Cycle 1, the dose of BXCL701 will be escalated to a total daily dose of 0.6 mg in the next cohort of 3 patients.

- If ≥1 of the 3 original patients has a DLT in Cycle 1, after a discussion between the sponsor and the investigator, either 3 patients (if 1 patient experiences a DLT) or 6 to 9 patients (if 2 or 3 patients experience a DLT) will be added at the 0.4 mg BXCL701 dose level. For this expanded 0.4 mg cohort:
    - If less than one third of the patients experience a DLT, consideration will be given to dose escalation to 0.6 mg BXCL701 plus PEMBRO.
    - If one third of the patients experience a DLT, the Phase 2a can commence.
    - If more than one-third of the patients experience a DLT, a discussion will be held between the investigator and sponsor as to how to proceed.

Following dose escalation to 0.6 mg BXCL701 plus PEMBRO in 3 patients:

- If there are no DLTs at this dose level, the Phase 2a can commence.
- If ≥1/3 patients have a DLT in Cycle 1, after a discussion between the sponsor and the investigator, 6 to 9 patients will be added at the 0.6 mg BXCL701 total daily dose level; and consideration of an alternate dosing (e.g., split dose) schedule may be given.
- For this additional cohort of 6 to 9 patients:
    - If less than or equal to one-third of the patients experience a DLT, the Phase2a can commence.
    - If more than one third of the patients experience a DLT, consideration will be given to the use of a 0.4 mg total daily dose of BXCL701, or an intermediate dose, plus PEMBRO in the Phase 2a.

Patients in the Phase1b who do not meet the criteria for discontinuation will be allowed to continue treatment. Once the recommended dosing regimen of BXCL701 for the Phase 2a is determined, any patients still tolerating treatment in a lower BXCL701 dose cohort may have their BXCL701 doses escalated to the recommended dosing regimen with the start of the next cycle at the investigator's discretion.

The study schema is presented in Figure 1.

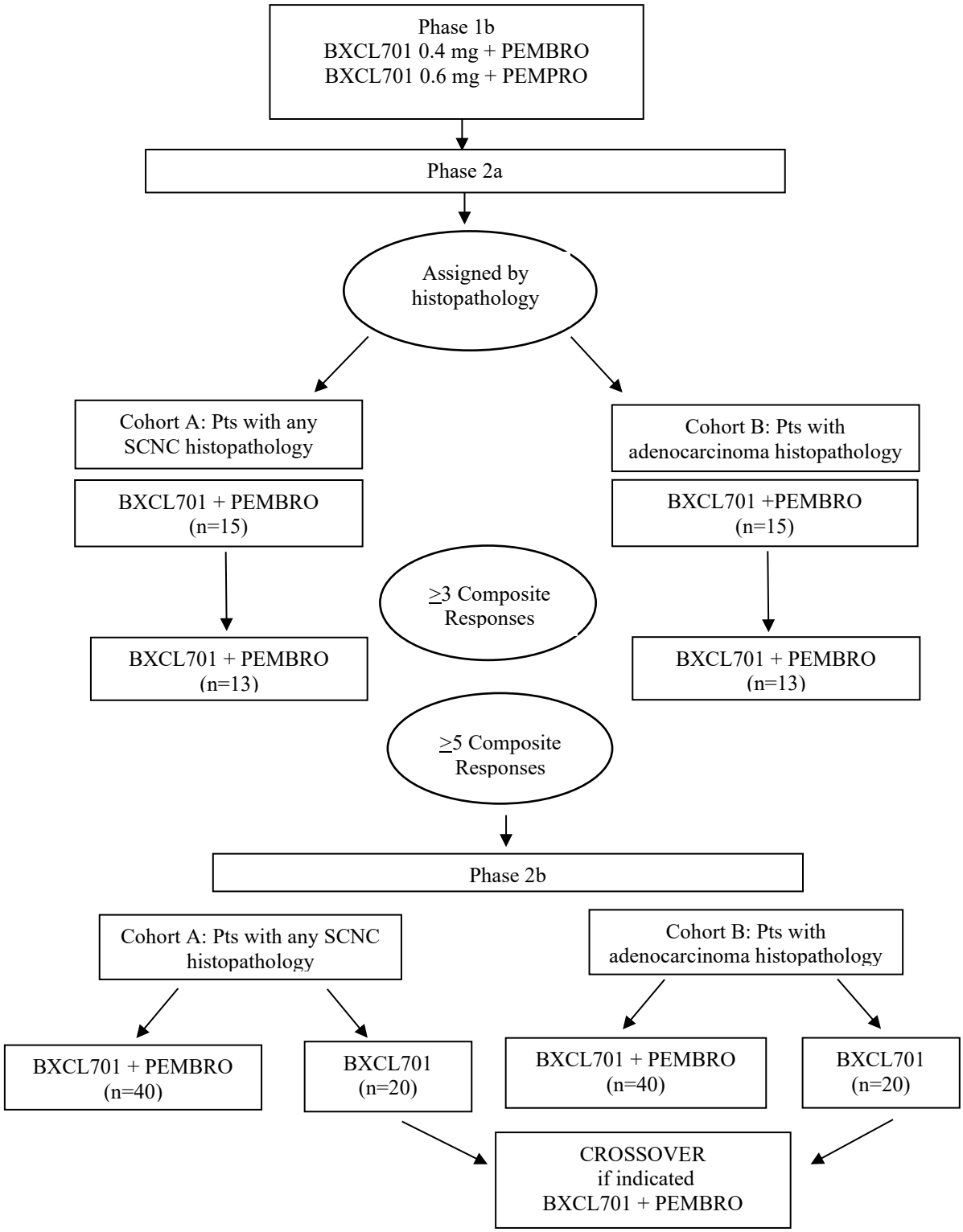
A Safety Review Committee, which will be comprised of both investigators and sponsor representatives, will review the safety during the Phase 1b and during the trial before the Phase 2a begins. If an intermediate dose is selected for the Phase 2a, the committee will monitor the first 6 patients enrolled in the Phase 2a through Cycle 1.

All safety data from all patients enrolled in each cohort will be reviewed to confirm any DLTs that were experienced and to determine enrolling the next cohort, as well as the BXCL701 dosing regimen to be used in the Phase 2b. Unless doses were held because of AEs, a patient must have received >70% of his BXCL701 doses in Cycle 1 (e.g., ≥10 of 14 planned doses) with PEMBRO dosed on Day 1 of Cycle 1 to be eligible for DLT assessment.

Toxicities will be assessed by the investigator using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5. The relationship of an

AE to combination therapy (i.e., attribution to BXCL701 and/or PEMBRO) is to be assessed by the investigator using the criteria in the protocol (Section 5.3.1).

Figure 1 Study Schematic



Abbreviations: mCRPC = metastatic castration-resistant prostate cancer; n = number of patients; PEMBRO = pembrolizumab; Pts = participants; SCNC = small cell neuroendocrine prostate cancer; NEP = neuroendocrine prostate cancer.

A DLT is defined as any of the following AEs occurring during Cycle 1, regardless of investigator attribution to study treatment, unless the AE can be clearly and incontrovertibly attributed to an extraneous cause (e.g., PD) by the Principal Investigator PI):

- Any Grade 4 laboratory abnormality, regardless of duration.
- Any Grade 3 non-hematologic AE, with the exceptions of Grade 3 nausea, vomiting, diarrhea, constipation, fever, fatigue, skin rash, or non-clinically significant laboratory abnormality that resolves to Grade ≤2 within 72 hours with optimal medical management.
- Grade 3 thrombocytopenia with Grade >1 bleeding or requirement for platelet transfusion.
- Grade 3 febrile neutropenia.
- Grade 3 fever.
- Grade 3 skin rash.
- Laboratory abnormalities meeting Hy's law criteria (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] >3 × upper limit of normal [ULN] with concomitant total bilirubin > 2 × ULN).
- Grade 3 transaminase (AST/ALT) elevation.
- Any toxicity resulting in ≥30% held/skipped doses of BXCL701 during Cycle 1.
- Delay of Cycle 2 by ≥14 days due to toxicity.
- Any other significant toxicity considered by the investigator and sponsor's medical representatives to be dose-limiting.

Phase 2a:

After assessment of the safety and confirmation of the BXCL701 + PEMBRO dose regimen to be used in the subsequent stage, the Phase 2a will begin. Eligible patients will receive BXCL701 on Days 1 to 14 of a 21-day cycle plus PEMBRO 200 mg administered IV on Day 1 of every 21 days.

Phase 2b:

Upon the completion of the Phase 2a and achievement of the protocol required composite responses for a given histologic subtype, the Phase 2b enrollment will begin for that subtype. Eligible patients will be randomized 2:1 to receive either the following, respectively:

- Combination therapy of BXCL701 on Days 1 to 14 of a 21-day cycle plus PEMBRO 200 mg administered IV on Day 1 of every 21 days.
- Monotherapy BXCL701 on Days 1 to 14 of a 21-day cycle. Upon radiographic disease progression with monotherapy, crossover to combination treatment is allowed.

Study Design Features (Both Phases):

In both the Phase 1b and the Phase 2a, patients will be screened for study eligibility within 28 days before the first study drug dose after provision of written informed consent. Patients who are determined to be eligible, based on Screening assessments, will be enrolled in the study on Cycle (C)1, Day (D)1 (baseline, before the first dose of BXCL701).

During treatment, patients will attend study center visits and have study evaluations performed as detailed in the Schedule of Assessments (Table 2). All study visits will be conducted on an outpatient basis but may be conducted on an inpatient basis per the investigator's judgement.

All patients must have pre-treatment (prior to study treatment dosing) imaging (computed tomography [CT] scan of chest/abdomen/pelvis or magnetic resonance imaging [MRI] for baseline tumor measurements, as well as bone scintigraphy [BS]). Patients with skin, subcutaneous, or lymph node metastases may also have tumor evaluations (including measurements with a ruler) by means of physical examination. Patients with a history of central nervous system (CNS) malignant involvement or CNS symptoms should have either CT or MRI imaging of the brain performed to assess active CNS malignancy.

Tumor measurements and disease response assessments (CT or MRI; BS) are also to be performed at the end of Cycle 3 (approximately 9 weeks after the first study treatment dose), and then approximately every 9 weeks thereafter until development of PD. Patients on monotherapy, with evidence of radiographic progression, may crossover to receive the combination. For patients with evidence of disease control (stable disease or better) at Week 27, tumor measurements and disease response assessments may be performed less frequently (approximately every 12 weeks) thereafter. Tumor measurements and disease response assessments also are to be performed at the End of Treatment (EOT) visit.

Additionally, measurement of serum PSA will be performed on Day 1 of every treatment cycle.

Population pharmacokinetics of BXCL701 will be assessed using sparse pharmacokinetic sampling.

Patients may continue to receive treatment until the development of radiographic progression by RECIST 1.1/Prostate Cancer Working Group 3 (PCWG3) criteria, unequivocal clinical progression, unacceptable toxicity, another discontinuation criterion is met, or closure of the study; no maximum duration of therapy has been set. Patients with PSA progression in the absence of radiographic or clinical progression should continue to receive protocol therapy. Treatment may continue beyond the first radiographic progression if there is clinical benefit (Section 7.3.2.3).

All remaining patient samples at the end of the study will be de-identified with respect to the patient and moved into long-term storage for up to 5 years for future analysis, after which time the samples will be destroyed.

Phase 2a only:

Numeration of CTCs by Veridex assay will be performed at pre-dose (-2 hours) on C1D1, C2D1, C4D1 and every 3 cycles thereafter until the EOT visit.

3.1. Justification for Dose

In a previously conducted multiple dose clinical study by Point Therapeutics with single agent BXCL701 (CA168-002), there was a dose-dependent increase in plasma IL6 in subjects receiving daily doses of BXCL701 from 0.3 to 1.2 mg when measured on Day 7. At doses ≥0.1 mg, pronounced inhibition of plasma CD26/DPP4 activity to ≤20% of baseline was apparent within 1 hour of dosing; and at doses of 0.3 mg, CD26/DPP4 activity was almost completely inhibited (>95%) within 30 minutes of the first dose on Day 1. These pharmacologic data suggest that daily doses of 0.4 to 0.6 mg BXCL701 provide maximum pharmacodynamic inhibition, as measured by

inhibition of plasma CD26/DPP4, while also providing significant cytokine (IL6 and granulocyte-colony stimulating factor [GCSF]) upregulation over baseline.

BioXcel has considered the clinical AE profile of each therapeutic, BXCL701 and PEMBRO, to clinically combine them. Based upon results from completed clinical trials, single agent BXCL701 is associated with AEs that are generally mild, manageable, and reversible. The most frequently observed AEs that appear to be characteristic of BXCL701 are edema/peripheral swelling, hypotension, dizziness, and hypovolemia. These events, including edema, tend to be manageable and reversible and usually resolve following a drug hold. The most common AEs associated with PEMBRO include anemia, fatigue, hyperglycemia, hyponatremia, itching, cough, and nausea. A comparison of the safety profiles of BXCL701 and PEMBRO does not indicate clinically significant overlapping potential toxicities. Given the lack of overlapping toxicities when the 2 agents are combined, it is expected that there will be no more toxicity than the sum of the individual toxicities observed at the maximum tolerated dose of each agent. Nonetheless, the starting dose for BXCL701 in combination with PEMBRO is proposed to be 0.4 mg, i.e., 67% of the recommended Phase 2 dose (0.6 mg daily dose) previously defined by Point Therapeutics in combination with several other therapeutics.

3.2. Justification for Alternate Dose Schedule

Over 700 subjects/patients have received doses of BXCL701 ranging from 0.01 mg to 2.4 mg daily. Of these, 585 were cancer patients, and approximately 500 of these patients received BXCL701 concomitantly with standard chemotherapy treatment. In these studies, BXCL701 was usually administered BID. Twice daily dosing was generally well tolerated in these prior studies in combination with chemotherapy. In the previous Study CA168-102, a 7-day, BID, dose-escalation study designed to evaluate the safety, PK, and pharmacodynamics of multiple oral doses of talabostat in healthy volunteers, individual doses of ≥ 0.3 mg were required to achieve > 95% inhibition of DPP4 activity in plasma. The activity of DPP8/9, measurable in tissue only, was not assessed. In the only prior single agent study conducted in cancer patients, PTH-301, an open-label, single-arm, 2-stage, multicenter, Phase 2 study in patients with Stage IV melanoma, 2 patients achieved objective responses (1 CR and 1 PR) at the total daily dose of 0.6 mg (administered as 0.3 mg BID), with 1 patient tolerating dose escalation to a 0.8 mg total daily dose (administered as 0.4 mg BID).

The once daily (QD) dose was explored initially in this study in order to assess the safety and tolerability of a more convenient schedule when given with pembrolizumab rather than standard chemotherapy. Among the 3 patients treated at the dose level of BXCL701 0.6 mg QD, Days 1 to 14 of 21-day cycle, + pembrolizumab 200 mg IV on Day 1 of a 21-day cycle, 1 patient experienced a DLT of Grade 3 syncope during the DLT period. One patient experienced Grade 5 acidosis outside of the DLT period. Due to the DLT, the lead-in dosing cohort of 0.6 mg per day will be expanded to add an additional 6 patients as required by the protocol. In addition, as allowed in Protocol Section 6.1, the dosing schedule will be adjusted to split the total daily dose into a morning dose and an evening dose, consistent with the BID dosing schedule used in the prior studies with chemotherapy. Splitting the dose will potentially improve tolerability while maintaining the total daily dose previously associated with objective responses.

Based on the experience of the Phase 1b cohort receiving BXCL701 at a 0.6 mg total daily dose, the Safety Review Committee may alternately recommend that the BXCL701 dose for the Phase 2a be reduced to a 0.4 mg total daily dose, or an intermediate dose.

3.2.1. Justification for Step-Up Dosing in Efficacy Phase

Based on a review of emerging data, the dosing schedule in the Phase 2 will be modified to implement a step-up dosing schedule during Cycle 1. The intent of step-up dosing is to immediately address a potentially serious side effect of hypotension that appears most likely to occur during the first week of treatment in Cycle 1. The Sponsor has evaluated 0.4 mg total daily dose during Phase 1b of this study and it was well-tolerated, with no DLTs experienced. In the Phase 1b cohort, none of the three patients experienced adverse events consistent with cytokine activation considered related to BXCL701. Therefore, the Sponsor believes that requiring a one-week lead-in dosing period of 0.2 mg BID may potentially mitigate the effects of cytokine activation, including hypotensive events, which seem to predominantly occur during the first week of treatment. Escalation to 0.3 mg BID in patients demonstrating tolerance after one week of treatment is important since it is the dose that was previously associated with objective responses during prior development of BXCL701 (talabostat).[17]

3.3. Justification for Patient Population

Immunotherapies aimed at the PD-1 receptor, or its ligand have demonstrated clinical activity across multiple tumor types. However, clinically relevant benefit of single agent PD-1 targeted therapy has not been demonstrated in mCRPC. Prostate cancer is, therefore, considered a “cold” tumor characterized by minimal T-cell infiltrates and very limited response to single-agent PD-1 targeted therapy.[18] Resistance to immune therapy in “cold” tumors can be driven by absence of relevant immune cells (immune desert).[19] Activation of innate immunity may increase sensitivity to immune checkpoint inhibitors.[20] BXCL701 can induce an innate immune reaction and tumor inflammation, potentially leading to synergistic anticancer activity when combined with the immune checkpoint PD-1 targeted antibody, pembrolizumab. Preclinical data in an MC38 mouse model of colon adenocarcinoma has shown a synergistic anti-tumor effect on tumor growth inhibition with BXCL701 and anti-PD-1 combination therapy.[21]

Initial safety of the combination therapy has been demonstrated in the Phase 1b portion of this study, from which the RP2D was determined. The Phase 1b included a total of 13 patients with mCRPC; 8 patients with predominant adenocarcinoma phenotype and 5 patients with SCNC, respectively. Additionally, as of 08-May-2020 in the Phase 1b of this trial, among the 13 patients treated with the combination of BXCL701 at various doses and schedules plus pembrolizumab 200 mg q3 weeks, 1 of 8 patients with predominant adenocarcinoma phenotype has achieved a confirmed PSA response with stable disease and an additional patient had stable disease by PSA for 9 months (unpublished interim results).

In summary, despite innovations in cancer treatment, alternative therapies are needed for patients with mCRPC. Patients with predominant adenocarcinoma phenotype have a number of systemic treatment options, however, the disease invariably progresses. Patients with small cell neuroendocrine phenotype have even fewer effective treatment options, essentially limited to chemotherapy. Therefore, an unmet need remains for both subsets of patients.

4. STUDY POPULATION

Approximately 6 to 12 evaluable patients with mCRPC will be enrolled in the Phase 1b of the study. A total of between 30 and 56 evaluable patients will be enrolled across 2 separate Cohorts in the Phase 2a of the study with approximately 15 to 28 evaluable patients with SCNC and approximately 15 to 28 evaluable patients with adenocarcinoma phenotype.–Recruitment may occur until 15 evaluable patients are identified in each cohort of the Stage 1 cohorts of Phase 2a and until 13 evaluable patients are identified in each of the Stage 2 Cohorts of the Phase 2a. Phase 2b will include up to 60 evaluable patients with each SCNC and adenocarcinoma phenotypes, and recruitment may continue until 60 evaluable patients are identified.

4.1. Eligibility Criteria

All patients must satisfy the following inclusion and exclusion criteria to be eligible for entry into the trial.

4.1.1. Inclusion Criteria

1. Patient has evidence of progressive mCRPC, as defined by PCWG3 criteria.
   a. Patients with de novo small cell prostate cancer are not required to have received androgen deprivation therapy (ADT).
2. Progression during or following completion of at least 1 prior line of systemic therapy for locally advanced or metastatic prostate cancer.
3. Phases 2a and 2b only:
   SCNC – Cohort A of Phase 2a; not applicable to Phase 2b:
   a. Patient has histologic evidence of SCNC either with archival tissue or a fresh tumor biopsy obtained during Screening. Archival or fresh tumor biopsy tissue must be submitted for a central laboratory pathology review; however, enrollment can proceed if SCNC is determined by a local pathology review.
   b. Patient has previously received at least 1 prior line of cytotoxic chemotherapy. Patients who either have refused chemotherapy or are considered unsuitable for chemotherapy may be eligible following discussion with the sponsor.
   c. Must be willing to undergo metastatic tumor biopsy during Screening. Requirement may be waived in patients without a safely accessible lesion or for patients with evaluable archival metastatic tumor tissue.
   d. Has measurable disease per RECIST 1.1 criteria.

   Adenocarcinoma - Cohort B of Phase 2a; randomized population for Phase 2b:

   a. Patient has histologically or cytologically confirmed adenocarcinoma of the prostate without small cell neuroendocrine features.
   b. Patients with soft tissue disease must provide a fresh core or excisional biopsy or archival tissue from a site not previously irradiated for central pathology review; however, enrollment may proceed if predominant adenocarcinoma without small cell neuroendocrine features is determined by local pathology review.
   c. Has been treated with at least 1 but no more than 2 second generation AR pathway target agents (e.g., abiraterone acetate and/or enzalutamide or other next generation agent) and at least 1 regimen/line of taxane containing chemotherapy in the metastatic

castration-sensitive prostate cancer (mCSPC) or mCRPC setting. Patients with known actionable mutations should have progressed on applicable standard care targeted therapy or have documented intolerance to or be unsuitable for such therapy.

d. RECIST 1.1 measurable disease or detectable bone metastases by whole body bone scintigraphy.

4. Patient has serum testosterone <50 ng/dL during Screening except for those with de novo small cell prostate cancer.
   a. Patients with treatment-emergent SCNC without a history of bilateral orchiectomy are required to remain on luteinizing hormone-releasing hormone (LHRH) analog during the course of protocol therapy except for patients with de novo small cell prostate cancer.
5. Patient has an ECOG performance status of 0-2.
6. Patient is ≥18 years of age.
7. Patient's acute toxic effects of previous anticancer therapy have resolved to ≤Grade 1 except for Grade 2-3 peripheral neuropathy or any grade of alopecia.
8. Patient has adequate baseline organ function, as demonstrated by the following:
   a. Serum creatinine (Cr) ≤1.5 times institutional upper limit of normal (ULN) or calculated Cr clearance >50 mL/min.
   b. Serum albumin ≥2.5 g/dL.
   c. Total bilirubin ≤1.5 × ULN.
   d. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × institutional ULN (patients with hepatic metastases must have AST/ALT ≤5 × ULN).
9. Patient has adequate baseline hematologic function, as demonstrated by the following:
   a. Absolute neutrophil count (ANC) ≥1.5 × 10^9/L;
   b. Hemoglobin ≥8 g/dL and no red blood cell transfusions during the prior 14 days;
   c. Platelet count ≥100 × 10^9/L and no platelet transfusions during the prior 14 days.
10. Male patients and their female partners of childbearing potential must agree and commit to use a barrier contraception (e.g., condom with spermicide throughout the duration of the study until at least 6 months following the last dose of study drug, in addition to their female partners using either an intrauterine device or hormonal contraception and continuing until at least 6 months following the last dose of study drug. This criterion may be waived for male patients who have had a vasectomy >6 months before signing the informed consent form. [Note: In the United States, female partners of study participants are not required to use contraception as a condition of their partner's eligibility, but female partners with childbearing potential should consider use of effective methods of contraception for the duration of their male partner's study participation and for at least 6 months following the last dose of study medication.
11. Patient has signed informed consent prior to initiation of any study-specific procedures or treatment.
12. Patient is able to adhere to the study visit schedule and other protocol requirements, including follow-up for OS.

4.1.2. Exclusion Criteria

1. Patient has received treatment with >2 cytotoxic chemotherapy regimens for castration-resistant prostate cancer (CRPC). Chemotherapy in the hormone-sensitive setting does not count in this assessment provided the last dose was >6 months before study entry. A change in chemotherapy agents due to intolerance after brief exposure may not count in this assessment, pending review with Medical Monitor.
2. Patient has received external-beam radiation or another systemic anticancer therapy within 14 days or 5 half-lives, whichever is shorter, prior to study treatment.
3. Patient has received treatment with an investigational systemic anticancer agent within 14 days prior to study drug administration.
4. Patient has received 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 (e.g., cytotoxic T lymphocyte–associated antigen 4 [CTLA-4], OX-40, CD137), or requires concomitant treatment with DPP4 inhibitors (e.g., gliptins).
5. Patient has an additional active malignancy that may confound the assessment of the study endpoints. If the patient has a past cancer history (active malignancy within 2 years prior to study entry) with substantial potential for recurrence, this must be discussed with the sponsor before study entry. Patients with the following concomitant neoplastic diagnoses are eligible: non-melanoma skin cancer and carcinomas in situ (including transitional cell carcinoma, anal carcinoma, and melanoma in situ).
6. Patient has clinically significant cardiovascular disease (e.g., uncontrolled or any New York Heart Association Class 3 or 4 congestive heart failure, uncontrolled angina, history of myocardial infarction, unstable angina or stroke within 6 months prior to study entry, uncontrolled hypertension, or clinically significant arrhythmias not controlled by medication).
7. Patient has QT interval corrected for heart rate using Bazett's formula (QTcB) >480 msec at Screening.
8. Patient has uncontrolled, clinically significant pulmonary disease (e.g., chronic obstructive pulmonary disease, pulmonary hypertension) that in the opinion of the investigator would put the patient at significant risk for pulmonary complications during the study.
9. Patient has brain or leptomeningeal metastases that are symptomatic and progressive on imaging. Patients with a history of CNS metastases must have received appropriate treatment. Central nervous system imaging is not required prior to study entry unless there is a history of CNS involvement or clinical suspicion of CNS involvement. Imaging of patients with a prior history of CNS metastases should be compared to prior imaging to discern PD.
10. Patient has an active autoimmune disease or Grade ≥3 (non-infectious) pneumonitis that has required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) or treatment with drugs (e.g., neomercazol, carbimazole) that function to decrease the generation of thyroid hormone by a hyperfunctioning thyroid gland

(e.g., in Graves' disease) is not considered a form of systemic treatment of an autoimmune disease.

11. Patient has a diagnosis of immunodeficiency or is receiving systemic steroid therapy at a prednisone equivalent dose of >10 mg daily for at least 1 week or other form of immunosuppressive therapy within 7 days prior to Cycle 1 Day 1 (C1D1).
12. Patient has uncontrolled intercurrent illness including, but not limited to, uncontrolled infection, suspected or active Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection, disseminated intravascular coagulation, or psychiatric illness/social situations that would limit compliance with study requirements.
13. Patient has known positive status for human immunodeficiency virus, active or chronic Hepatitis B, or Hepatitis C. Screening is not required.
14. Patient has any medical condition that, in the opinion of the investigator, places the patient at an unacceptably high risk for toxicity.
15. Any dysphagia, odynophagia, esophageal dysmotility or stricture, known GI malabsorption syndrome, or intractable diarrhea that may significantly alter the absorption of orally administered study drug.
16. Patients with history of symptomatic orthostatic hypotension within 3 months prior to enrollment. Orthostatic hypotension is defined as a drop in systolic blood pressure (BP) of ≥20 mmHg or diastolic BP of ≥10 mmHg with assumption of an upright posture.

5. STUDY METHODOLOGY

Approximately 6 to 12 evaluable patients with mCRPC will be enrolled in the Phase 1b of the study.

In Phase 2a eligible participants will be assigned to Cohort A (SCNC) or Cohort B (adenocarcinoma without small cell histology) based on histology/cytology. Approximately 15 to 28 evaluable patients will be enrolled in each cohort. A minimax 2-stage Simon design will be applied separately for each cohort. In the first stage, 15 evaluable patients will be accrued. If there are 2 or fewer composite responses in these 15 patients, accrual to the study arm will be halted. Otherwise, 13 additional evaluable patients will be accrued for a total of 28 patients. A composite response is defined as 1 or more of the following:

- Objective response by RECIST 1.1 criteria.
- CTC conversion from ≥5/7.5 mL to <5/7.5mL per Veridex assay
- 50% or greater PSA decline from baseline.

The tabular Study Schedule of Assessments is found in Appendix A (Section 11). The description of Detailed Study Procedures by visit is found in Appendix B (Section 12).

During the Screening period, patients who have signed a consent form will be evaluated to ensure they meet inclusion and exclusion criteria. Patient demographics, performance status, and disease staging will be collected. Vital signs (both sitting and standing blood pressure, heart rate, body temperature, and respiratory rate), physical examination, electrocardiogram (ECG), and clinical laboratory evaluations (complete blood count plus differential, serum chemistry, liver function

tests, and urinalysis) will be performed at Screening and baseline and will be monitored throughout the treatment period. Patients meeting the study entry criteria will begin study treatment within 4 weeks of the Screening visit. At the discretion of the investigator, patients with out-of-range clinical laboratory evaluation values at Screening may be retested within the Screening period if the investigator believes that the retest values may be in range and allow inclusion in the study.

Patients will undergo tumor assessment, which must include cross-sectional imaging (MRI or CT scanning with IV contrast whenever possible) of the chest/abdomen/pelvis plus whole-body bone scan. Other body sites (e.g., neck) will be included as clinically indicated. Tumor assessment will be performed at Screening, C4D1 (± 7 days), C7D1 (± 7 days), C10D1 (± 7 days), and Day 1 (± 7 days) of every 3rd cycle thereafter.

The same imaging method used to determine index lesion size at baseline must be used to follow lesion size throughout the study. Assessments will be conducted throughout the treatment Phase as described in Appendix A (Section 11) and Appendix B (Section 12).

Adverse events, clinical laboratory assessments, PSA, and concomitant medications will be monitored and recorded throughout the entire study period.

Patients may continue to receive study treatment until the development of radiographic or clinical progression, unacceptable toxicity, another discontinuation criterion is met, or closure of the study by the sponsor; no maximum duration of therapy has been set. Treatment beyond progression will be allowed; see Section 5.8 for details.

Patients will complete an End of Treatment (EOT) visit prior to crossover (if applicable) and upon discontinuation of study treatment, within 21 days after their last dose of study drug. Upon discontinuation of study treatment, Safety Follow-Up is to be conducted 30 days (± 7 days) after their last dose of study drug as well as additional subsequent time points if drug-related AEs have not yet resolved. Patients will also be contacted by telephone approximately every 90 days for clinical evidence of PD in settings in which discontinuation of study therapy was for reasons other than PD (tumor measurements as specified in the protocol are not required after the EOT visit), and for assessment of survival status. This extended follow-up for disease status and survival after discontinuation of study treatment will continue for up to 12 months after study treatment is discontinued.

The 2b portion of the study eligible participants will be mCRPC patients with either adenocarcinoma without small cell histology or SCNC. 60 patients of each histology will be enrolled and randomized 2:1 to either combination therapy BXCL701 + PEMBRO or PEMBRO monotherapy. A response will be defined as described in RECIST 1.1 guidelines.

5.1. Concomitant Medications

5.1.1. Permitted Medications/Therapies

All medications taken within 3 months of study start and used throughout the study must be recorded in the appropriate section of the patient's electronic case report form (eCRF).

Patients who have not had prior bilateral orchiectomy must continue LHRH analogue treatment to maintain castrate level of testosterone during the course of study treatment (except for patients with de novo small cell prostate cancer).

The use of bone-modifying agents (e.g., zoledronic acid, denosumab) is permitted as clinically indicated.

The use of growth factors (e.g., G-CSF) is allowed as clinically indicated for the treatment of Grade ≥3 cytopenia.

The use of any other systemic anti-cancer therapies other than outlined in the protocol is prohibited during the course of study treatment.

Preclinical studies have demonstrated a low potential for BXCL701 to inhibit the following major human liver CYP isoenzymes: CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 and it is mostly excreted unchanged, and is minimally metabolized. Further, relevant concentrations of BXCL701 did not induce CYP3A4 or CYP1A2; therefore, there are no prohibited medications based on CYP isoenzymes.

Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each AE, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to PEMBRO.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of the evaluation of the event.

- Pneumonitis:
    - For **Grade 2 events**, treat with systemic corticosteroids (e.g., oral prednisone 1 mg/kg or equivalent). When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
    - For **Grade 3-4 events**, immediately treat with IV steroids (e.g., solumedrol 1-2 mg/kg every 6-8 hours). Administer additional anti-inflammatory measures, as needed. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
    - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
- Diarrhea/Colitis:

Patients should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

- All patients who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be administered via IV infusion. For Grade 2 or higher diarrhea, consider gastroenterology consultation and endoscopy to confirm or rule out colitis.

- For **Grade 2 diarrhea/colitis**, administer oral corticosteroids (e.g., oral prednisone 1 mg/kg or equivalent). When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- For **Grade 3 or 4 diarrhea/colitis**, treat with IV steroids (e.g., solumedrol 1-2 mg/kg every 6-8 hours) followed by high dose oral steroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- Type 1 diabetes mellitus (T1DM) (if new onset, including diabetic ketoacidosis [DKA]) or ≥Grade 3 hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA):
  - For **T1DM** or **Grade 3-4** hyperglycemia
    - Insulin replacement therapy is recommended for T1DM and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
- Hypophysitis:
  - For **Grade 2** events, treat with corticosteroids (e.g., oral prednisone 1 mg/kg/day). When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids (e.g., solumedrol 1-2 mg/kg every 6-8 hours) for 24-48 hours, followed by high dose oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- Hyperthyroidism or hypothyroidism:

  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
  - **Grade 2** hyperthyroidism events and **Grade 2-4** hypothyroidism:
    - In hyperthyroidism, non-selective beta-blockers (e.g., propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy with levothyroxine or liothyronine is indicated per standard of care.

- **Grade 3-4** hyperthyroidism:
  - Treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- Hepatic:
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids (e.g., prednisone 1 mg/kg/day or equivalent).
  - For **Grade 3-4** events, treat with IV corticosteroids for 24 to 48 hours (e.g., solumedrol 1 - 2 mg/kg every 6-8 hours), followed by transition to oral high dose steroids (e.g., prednisone 1 mg/kg/day or equivalent).
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.
- Renal Failure or Nephritis:
  - For **Grade 2** events, treat with oral corticosteroids (e.g., prednisone 1 mg/kg/day).
  - For **Grade 3-4** events, treat with IV corticosteroids (e.g., solumedrol 1 - 2 mg/kg every 6 - 8 hours) for 24 - 48 hours followed by transition to oral high dose steroid (e.g., prednisone 1 mg/kg/day or equivalent).
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Management of Infusion Reactions:

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Table 1 shows treatment guidelines for patients who experience an infusion reaction associated with the administration of PEMBRO.

Table 1 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction: infusion interruption not indicated; intervention not indicated.	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator.	None.
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hr.	**Stop infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids, antihistamines, NSAIDS, acetaminophen, narcotics. Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise, dosing will be held until symptoms resolve, and the patient should be premedicated for the next scheduled dose.	Patient may be premedicated 1.5 hr (±30 minutes) prior to infusion of pembrolizumab with: • Diphenhydramine 50 mg po (or equivalent dose of antihistamine). • Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates). Grade 4: Life-threatening; pressor or ventilatory support indicated.	**Stop infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids, antihistamines, NSAIDS, acetaminophen, narcotics, oxygen pressors, corticosteroids, epinephrine. Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Patient is permanently discontinued from further trial treatment administration.**	No subsequent dosing.
Appropriate resuscitation equipment should be available in the room, and a physician should be readily available during the period of drug administration.		

IV = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NSAID = non-steroidal anti-inflammatory drug; po = per os (oral).

5.1.2. Prohibited Medications/Therapies

Enrolled patients may not receive investigational or approved anticancer agents including cytotoxic chemotherapy agents, anticancer tyrosine kinase inhibitors, or therapeutic monoclonal antibodies.

All DPP4 inhibitors (e.g., gliptins) are prohibited.

Palliative radiation is not permitted during study enrollment unless it is being performed for an existing, nonprogressive metastasis/symptoms and involves a narrow radiation port (e.g., solitary bone lesions).

5.2. Efficacy Assessments

5.2.1. Primary Efficacy Parameter

Phase 2a

- The primary efficacy parameter is the composite response rate defined as achieving 1 or more of the following:
  - Objective response by RECIST 1.1 criteria.
  - CTC conversion from ≥5/7.5 mL to <5/7.5 mL per Veridex assay.
  - 50% or greater PSA decline from baseline

Phase 2b

- The primary efficacy parameter is the response rate defined by RECIST 1.1 guidelines.

5.2.2. Secondary Efficacy Parameters

Phase 2a

- Radiographic PFS.
- Prostate-specific antigen PFS.
- Overall survival (OS).
- Duration of response (DOR).
- Levels of cytokines previously shown to be modulated by BXCL701 in humans.

Phase 2b

- 50% or greater PSA decline from baseline
- Radiographic PFS.
- Prostate-specific antigen PFS.
- Overall survival.
- Duration of response.
- Levels of cytokines previously shown to be modulated by BXCL701 in humans.

5.2.3. Exploratory Efficacy Analyses

- To determine the response rate by iRECIST criteria with BXCL701 in combination with PEMBRO.
- To evaluate the quantitative and qualitative effects of BXCL701 in combination with PEMBRO on relevant immune effector cytokines and various immunological effector cells in blood and, whenever feasible, in tumor tissues.

- To explore the predictive value of baseline PD-L1 tumor expression in metastatic tumor tissue with subsequent clinical outcomes.
- To explore the relationship between baseline tumor mRNA immune profiling panel and clinical outcomes.
- To explore the relationship between baseline tumor genetic and protein expression features and clinical outcomes.

5.3. Safety Assessments

5.3.1. Non-Serious Adverse Events

An AE is any untoward medical occurrence in a patient participating in a clinical investigation, whether or not considered related to treatment. Patients should be instructed to report any AE that they experience to the investigator. Investigators should assess for AEs at each visit. All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the eCRF. Each AE is to be evaluated for duration, intensity, and causal relationship with the study treatment or other factors.

The investigator is responsible for monitoring the safety of patients who have entered the study. All AEs occurring during the treatment period and/or occurring within 30 days of the last dose of BXCL701 will be followed to the end of the study or until resolution. Adverse events will be graded according to the revised NCI CTCAE, Version 5.0, (see http://ctep.cancer.gov/reporting/ctc.html). Adverse events occurring 30 days after the last dose of BXCL701 do not need to be reported unless the investigator considers the event to be related to BXCL701.

Investigators are required to report to the sponsor or sponsor's representative all AEs experienced during the active treatment period of the clinical trial and for 30 days following the last dose of BXCL701. Serious AEs, as defined below, must be reported to the sponsor or sponsor's representative within 24 hours of first knowledge of the occurrence. All AEs that result in permanent discontinuation of study medication, whether serious or non-serious, must be reported to the sponsor.

Clinical laboratory data are to be collected in this study, and toxicity trends will be analyzed utilizing objective toxicity criteria. Abnormal laboratory findings considered clinically significant by the investigator and outside the expected deviation for a patient with mCRPC/SCNC should be reported as AEs, particularly if clinical action is required for the abnormality. Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the investigator and recorded on the eCRF. Clinical syndromes associated with laboratory abnormalities are to be recorded as such (e.g., diabetes mellitus instead of hyperglycemia). However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the investigator, it should be recorded as a separate AE on the eCRF.

Progressive disease (PD) should not be reported as an AE (see Section 5.7) unless the patient dies solely due to PD within 30 days of the last dose of BXCL701, in which case the AE term should be "Malignant Neoplasm Progression" and the AE outcome should be reported as "death".

The relationship of each AE to each study drug (BXCL701 and/or PEMBRO) will be evaluated by the investigator using the following definitions:

- Not related: The AE is clearly not related to the study drug(s). The AE can be explained to be likely related to other factors such as concomitant medications or the patient's clinical state.
- Possibly related: The AE may be related to the investigational agent(s). A plausible temporal sequence exists between the time of administration of the investigational product and the development of the AE, and it follows a known response pattern to the investigational product. The reaction may have been produced by the patient's clinical state or other concomitant therapies or interventions.
- Related: The AE is clearly related to the investigational agent(s). A plausible temporal sequence exists between the time of administration of the investigational product and the development of the AE, and it follows a known response pattern to the investigational product. The occurrence of this AE can be confirmed with a positive re-challenge test or supporting laboratory data.

The causality criteria of related and possibly related will be considered "related" to the study drug(s) for regulatory reporting requirements.

5.3.2. Serious Adverse Events

An SAE is any adverse experience that suggests a significant hazard, contraindication, side effect, or precaution. This includes any experience that:

- Results in death.
- Is life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Medically significant events that do not meet the precise definitions above may be considered SAEs when, based upon clinical judgement, the patient is at risk for long-term- sequelae or requires immediate, acute treatment of the event to mitigate long-term sequelae. Examples of such events include allergic bronchospasm requiring intensive treatment, seizures, stroke, anaphylaxis, or blood dyscrasias.

Hospitalizations or prolonged hospitalizations for elective procedures or additional monitoring, as described in section 6.1, will not be considered SAEs.

5.3.3. Reporting Serious Adverse Events

Serious AEs occurring after the patient has provided informed consent, but before the first dose of study treatment, will be collected as medical history unless the event is either new and attributed to protocol-mandated procedures by the Investigator, or there is a significant change in the rate of occurrence or an increase in the severity of the pre-existing condition which is judged to be clinically important and attributed to the protocol-mandated procedures by the Investigator. Any

SAE or death occurring during the treatment period and/or within 30 days following the last dose of study medication must be reported to IQVIA™ Biotech within 24 hours of first knowledge of the occurrence. The site should submit an SAE form within 24 hours to IQVIA™ Biotech Safety. If any SAE occurs, study treatment should be interrupted or discontinued at the discretion of the physician investigator.

IQVIA Biotech Safety Email: safety-inbox.biotech@iqvia.com

IQVIA Biotech Safety Phone: 919-313-7111 (US Toll-Free: 866-758-2798)

IQVIA Biotech Safety Fax: 919-313-1412 (US Toll-Free: 866-761-1274)

IN THE CASE OF LIFE-THREATENING AES, OR IN THE EVENT OF DEATH UNRELATED TO PD, THE CLINICAL REPRESENTATIVE MUST BE CONTACTED IMMEDIATELY:

[redacted]

Office: [redacted] Mobile: [redacted]

The investigator will be requested to supply detailed information regarding the event at the time of the initial contact. All SAEs must be reported to the reviewing Institutional Review Board (IRB) per the IRB's standard operating procedures, and a copy of that report must be forwarded to the sponsor or sponsor's representative.

5.4. Adverse Event Follow-Up

Patients are to be monitored for AEs throughout the treatment period and for a minimum of 30 days after their last dose of BXCL701. Longer AE follow-up is required, if necessary, to document recovery from AEs considered related to study medication. For patients who discontinue study medication due to an AE, repeated observations of that AE (or laboratory abnormality) must be made at intervals not exceeding 30 days until recovery is documented.

No further reporting of new AEs is required after the initiation of any subsequent chemotherapy or more than 30 days following the last dose of study medication, unless the study medication is considered to have contributed to the new AE.

5.5. Pharmacokinetic Assessments

Sparse pharmacokinetic sampling will be performed at the time points described in Appendix A (Section 11) for analysis of concentrations of BXCL701. Trough samples will be taken Pre-dose (-24hrs) on Day 1 of Cycles 1, 2 and 3. Samples will be taken within 30 minutes before the morning dose on Day 14 of Cycles 1, 2, and 3. For Cycle 1 only, a pre-dose sample will be taken within 30 minutes before the morning dose of Day 4 (+ 1 Day).

For Cycle 3 only, samples will be collected within 30 minutes before the morning dose is administered on Day 14 and at 2 hours (± 15 min), 6 hours (± 30 min), and if possible, 10-12 hours (optional draw if the patient or site cannot accommodate). Additional samples will be collected at these approximate times after the Day 14 evening dose: 10-14 hours, 60 hours (±24 hours), 108 hours (±24 hours), and 156 hours. The 156-hour sample will be collected within 30 minutes prior to the C4D1 dose. If C4 is not administered, the sample will be collected 156 hours after the last dose (±5 hours) (patient diary to be kept to record the number of doses the patient has taken in the cycle). Unscheduled PK assessments may be requested by the Sponsor in order to gather

additional information under certain conditions, for example, in the setting of an adverse event. Pharmacokinetic data will be analyzed using a population pharmacokinetic approach.

5.6. Pharmacodynamic Assessments

Whole blood samples will be collected at the time points described in Appendix A (Section 11) for analysis of relevant immune effector cytokines and various immunological effector cells in blood and tumor tissues. Unscheduled local cytokine assessments, if possible, may be performed based on clinical judgement or if requested by the Sponsor in order to gather additional information under certain conditions, for example, in the setting of an adverse event.

5.7. Progressive Disease

Worsening signs and symptoms of prostate cancer should be considered by the investigator as disease assessments are being made. Progressive disease is being assessed as an efficacy outcome in this study and should not be reported as an AE. However, deaths considered solely due to PD occurring within 30 days of the last dose of BXCL701 should be reported as an AE outcome with the AE term reported as "Malignant Neoplasm Progression."

5.8. Treatment Beyond Radiographic Progression

Accumulating evidence indicates that a minority of patients with solid tumors treated with immunotherapy may derive clinical benefit despite initial evidence of PD (due to "pseudo progression"). Patients will be permitted to continue on treatment beyond the initial RECIST 1.1-defined PD as long as they meet the following criteria:

- Investigator-assessed clinical benefit and without rapid PD.
- Patient continues to meet all other study protocol eligibility criteria.
- Patient tolerates study drug(s).
- Patient has a stable performance status.
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of PD (e.g., CNS metastases requiring immediate treatment).

The assessment of clinical benefit should consider whether the patient is clinically deteriorating and unlikely to receive further benefit from continued treatment. All decisions to continue treatment beyond initial progression must be discussed with the medical monitor, and an assessment of the risk/benefit of continuing with study drug(s) must be documented in the study records. The Informed Consent Form contains language explaining treatment beyond progression. If the investigator recommends continuing treatment following PD, the patient must be re-consented prior to continuing study drug.

For patients who stay on treatment beyond RECIST 1.1-defined progression, all study procedures (Table 2) should be performed continuously. A follow-up scan should be performed at the next scheduled imaging evaluation (but no sooner than 4 weeks) after the initial investigator assessed progression to determine whether there has been a decrease in the tumor size or continued progression. Patients will be discontinued from the treatment upon further evidence of progression.

5.9. Removal of Patients from the Study

Every effort within the bounds of safety and patient choice should be made to have each patient complete the treatment period of the study. Patients who have treatment discontinued due to PD may be treated with any additional therapy deemed appropriate by the investigator.

Patients may be discontinued from the study for any of the following reasons:

- Investigator recommends discontinuation and documents the reason(s).
- There is a need for any treatment not allowed by the protocol.
- Patient's decision to withdraw consent or discontinue for any reason.
- There is an unacceptable AE thought to be related to study medication.
- At the sponsor's request.

Any patient who discontinues during the treatment period should return to complete safety and disease assessments (see Appendix A [Section 11] and Appendix B [Section 12]).

5.10. Study Completion

The study will be considered complete when all patients have been followed to PD; are lost to follow-up, death, or withdrawal due to toxicity; patient's request; or investigator's discretion; and have completed all end-of-study treatment procedures.

6. STUDY MEDICATION

Study medication will be administered in 21-day cycles. Either BXCL701 or PEMBRO may be administered first. However, on Cycle 1 Day 1, it is recommended that PEMBRO be administered first and that ≥1 hour should elapse before the administration of BXCL701 so that it will be easier to determine the relatedness of any AEs to study drug.

6.1. BXCL701 Dosage and Administration

BXCL701 tablets contain valine-proline boronic acid formulated as the methanesulfonate salt. Current dosage strengths include 0.05-mg and 0.1-mg tablets for oral administration.

The starting dose regimen of BXCL701 (i.e., the dose regimen in Cohort 1) is 0.4 mg QD on Days 1 to 14 every 21 days. The BXCL701 dose regimen for any patient depends on the cohort in which the patient is enrolled in the Phase 1b. Additional dosing schedules may also be evaluated during the Phase 1b.

To minimize risk of hypotension, patients should be advised to maintain adequate hydration while on-treatment, such as drinking at least 2 liters of fluids per day, including fluids with electrolytes. Factors such as strenuous exercise, heat, humidity, fever, gastrointestinal disturbance may increase hydration needs. Administration of at least 1L of IV fluids is required at Cycle 1 Day 1. It is at the investigator's discretion to provide IV hydration during in-person clinic visits beyond Cycle 1 Day 1. The patient may be monitored overnight at the discretion of the Investigator. If the overnight monitoring is not associated with any Grade 2 or greater AE or any other SAE criteria, the admission will not be considered an SAE. Longer periods of in-patient monitoring may be implemented at the discretion of the Investigator.

Once the recommended dose for BXCL701 is determined, any patients still tolerating treatment in a lower BXCL701 dose cohort may have their BXCL701 doses escalated to the recommended dose regimen with the start of the next cycle at the investigator's discretion.

BXCL701 will be administered orally as 0.05-mg and 0.1-mg tablets. Patients will take the prescribed number of tablets on Days 1 to 14 of each cycle, for a total daily dose of 0.4 mg, 0.6 mg, or an intermediate dose. BXCL701 will be continued until PD or unacceptable toxicity. BXCL701 should not be taken on an empty stomach.

On days when pharmacodynamic studies are being performed, BXCL701 should be administered at the study center, and should be administered at (approximately) the same times of day on each treatment day in the cycle. In cycles in which pharmacodynamics are not evaluated, BXCL701 also should be administered at (approximately) the same times of day on each treatment day in the cycle.

6.1.1. Cycle 1 Dosing

On Cycle 1 Days 1 through 7, patients will be instructed to take 0.2 mg BID of BXCL701. On Cycle 1 Day 8, the patient will return to the clinic for a scheduled visit. During the visit, based on review of the patient's clinical labs, vital signs, and adverse events reporting, the patient's dose of BXCL701 can be escalated to 0.3mg BID. Patients should not be escalated to 0.3 mg BID of BXCL701 if they experienced any Grade >1 adverse event considered related to BXCL701 or skipped any doses due to hypotension or orthostasis during the first week of treatment. Investigators should contact the Sponsor to discuss these cases.

During the dosing period of Cycle 1, the patient will return to the clinic on Day 2 and Day 4 (+1 Day). During these visits, blood draws will be taken for pharmacokinetic and pharmacodynamic parameters, adverse events will be assessed, and vital signs will be measured prior to dosing. Patients will be instructed not to take their morning dose of BXCL701 until their vital signs have been taken and reviewed by the study physician.

Daily during the dosing period of Cycle 1, the patient will perform at home blood pressure monitoring at least twice daily, once in the morning and once in the late afternoon/evening. The patient will be provided with a log to record blood pressure measurements and will be asked to bring the log with them to every clinic visit during Cycle 1. The study team will contact the patient daily during treatment period of Cycle 1, through Day 14, to remind the patient of oral hydration guidelines, review side effects, and to review the patient's self-administered blood pressure measurements. The patient must take their blood pressure prior to dosing in the morning and evening. The patient will be instructed that they must not take their dose if their blood pressure is below 100 mmHg systolic or 50 mmHg diastolic. The patient must report any values below this to study physician immediately. The study physician will provide the patient further instruction as needed.

If the patient does not meet criteria to increase their dose to 0.3 mg BID during Cycle 1, they may continue on treatment at 0.2 mg BID until the investigator decides to escalate the patient's dose to 0.3 mg BID. During the first week of treatment at 0.3 mg BID, the patient will perform at home blood pressure monitoring at least twice daily, once in the morning and once in the late afternoon/evening, prior to dosing. The patient will record blood pressure measurements on a log

and will be asked to bring the log with them to every clinic visit during the first cycle that their dose is escalated to 0.3 mg BID. The patient will be instructed that they must not take their dose if their blood pressure is below 100 mmHg systolic or 50 mmHg diastolic. The patient must report any values below this to study physician immediately. The study physician will provide the patient further instruction as needed. The study team will contact the patient daily during the first week of treatment at the 0.3 mg BID dose level to remind the patient of oral hydration guidelines, review side effects, and to review the patient's self-administered blood pressure measurements.

6.2. Dose Adjustments of BXCL701 Secondary to Toxicity

BXCL701 dose modifications within a treatment cycle are not permitted in Cycle 1 in the absence of DLT. In Cycle ≥2, dose modifications within a treatment cycle will be at the discretion of the investigator. Doses should be taken at approximately the same time every day. Doses held because of AEs should not be made up on subsequent days within or following a cycle. A dose that is missed for reasons other than an AE (e.g., the patient forgets to take a dose) may be taken at least 6 hours prior to the next planned dose; otherwise, the missed dose may be administered on a day subsequent to the scheduled dose. Any additional adjustments should be discussed with the medical monitor or designee. If a dose is vomited within approximately 10 minutes of dosing, the patient may be re-dosed. If the patient vomits >10 minutes after dosing, no further attempts at dosing that particular dose should take place; dosing should resume with the next dose. Under no circumstances should missed doses be made-up when the patient is already taking a planned dose (i.e., no "doubling up" to account for missed doses).

If an SAE thought to be related to BXCL701 occurs during the treatment period, dosing of BXCL701 should be interrupted in that patient until the SAE resolves. If the investigator wishes to continue the patient on BXCL701, the medical monitor should be contacted to discuss continuing BXCL701 at the same or reduced dose.

The most frequently observed AEs that appear to be characteristic of BXCL701 are edema/peripheral swelling, hypotension, dizziness, and hypovolemia. These events, including edema, tend to be manageable and reversible and usually resolve following a drug hold. BXCL701 should be held for Grade 2 or higher episodes of such events, until resolution of these AEs. BXCL701 can be restarted at full dose after resolution of these AEs, including edema. For other Grade 2 or higher AEs deemed related to BXCL701, or for edema that has not responded to drug hold, the dose of BXCL701 can be reduced by 0.2 mg decrements of the total daily dose at the discretion of the investigator.

Discontinuation of BXCL701 should occur for any life-threatening AE, or for Grade 2 or higher treatment-related AEs that do not respond to dose reduction to a 0.2 mg total daily dose. If BXCL701 is discontinued due to an AE, all termination from treatment procedures and assessments must be performed.

6.3. Monitoring of Patient Compliance with BXCL701 Study Medication

All BXCL701 dosing containers must be returned to the clinic at each visit. Patients should be queried regarding their compliance with the dosing regimen, and medication containers should be reviewed at each visit to determine if any doses of BXCL701 have been missed, and the number

of missed doses recorded. Patients must be at least 70% compliant with taking BXCL701 in Cycles 1 and 2 in order to be included in the per-protocol efficacy analyses.

6.4. BXCL701 Description and Storage

BXCL701 is supplied as 0.1-mg tablets and 0.05-mg tablets in high-density polyethylene bottles with desiccant and child-resistant caps. The 0.1-mg tablets will be supplied as 90 tablets per bottle. The 0.05-mg strength will be supplied as 90 tablets per bottle. Supplies of BXCL701 will be appropriately labeled for clinical trial material. BXCL701 should be stored under refrigerated conditions between 2°C to 8°C (36°F to 46°F) until use. During the period of use, meaning once dispensed for patient, BXCL701 tablets may be stored in their original container for up to 30 days at room temperature, 15°-25°C (59°-77°F).

6.5. Pembrolizumab (PEMBRO)

PEMBRO is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. PEMBRO is currently indicated for the treatment of patients with unresectable or metastatic melanoma; for the first-line treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression; in combination with pemetrexed/platinum chemotherapy for the first-line treatment of patients with metastatic NSCLC irrespective of tumor PD-L1 expression; for the treatment of patients with metastatic NSCLC and PD on or after platinum-containing chemotherapy; for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma with PD on or after platinum-containing chemotherapy; and for the treatment of patients with refractory classical Hodgkin lymphoma, or who have relapsed after 3 or more prior lines of therapy.

The PEMBRO dose will be 200 mg, administered as an IV infusion over 30 minutes (±5 minutes) on Day 1 of each 21-day cycle. Premedication, according to standard local practices, is permitted.

6.6. Dose Modifications of Pembrolizumab

Dose modification of PEMBRO should be in accordance with the current Package Insert (Section 2.11) for AEs deemed related to PEMBRO as discussed here.

PEMBRO should be withheld for any of the following:

- Grade 2 pneumonitis (see US Package Insert - Warnings and Precautions Section 5.1).
- Grade 2 or 3 colitis (see Warnings and Precautions [Section 5.2]).
- Grade 3 or 4 endocrinopathies (see Warnings and Precautions [Section 5.4]).
- Grade 2 nephritis (see Warnings and Precautions [Section 5.5]).
- Grade 3 severe skin reactions or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) (see Warnings and Precautions [Section 5.6]).
- Aspartate aminotransferase or ALT > 3 to 5 × ULN or total bilirubin > 1.5 to 3 × ULN.
- Any other Grade 2 or 3 treatment-related adverse reaction based on the severity and type of reaction (see Warnings and Precautions [Section 5.7]).

Clinical investigators will be advised to resume PEMBRO in patients whose adverse reactions recover to Grade 0 or 1.

For AEs where causality is not evident, discussion of dose modification with the medical monitor is recommended.

6.7. Discontinuation of Pembrolizumab

Dose modification, including discontinuation, of PEMBRO, should be in accordance with the current Package Insert (Section 2.11).

Permanently discontinue PEMBRO for any of the following:

- Any life-threatening adverse reaction (excluding endocrinopathies controlled with hormone replacement therapy).
- Grade 3 or 4 pneumonitis or recurrent pneumonitis of Grade 2 severity (see Warnings and Precautions [Section 5.1]).
- Grade 3 or 4 nephritis (see Warnings and Precautions [Section 5.5]).
- Grade 4 severe skin reactions or confirmed SJS or TEN (see Warnings and Precautions [Section 5.6]).
- Aspartate aminotransferase or ALT > 5 × ULN or total bilirubin > 3 × ULN.
- For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by ≥50% relative to baseline and lasts for at least 1 week.
- Grade 3 or 4 myocarditis, encephalitis, or Guillain-Barré syndrome (see Warnings and Precautions [Section 5.7]).
- Grade 3 or 4 infusion-related reactions (see Warnings and Precautions [Section 5.8]);
- Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks;
- Persistent Grade 2 or 3 adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy) that do not recover to Grade 0 or 1 within 12 weeks after last dose of PEMBRO.

7. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

A Statistical Analysis Plan (SAP) will be written to address the analysis of data recorded in the clinical database as well as laboratory, pharmacokinetic, pharmacodynamic, and other data transferred to IQVIA Biotech. The analysis of safety Phase1b data to determine the BXCL701 dose to use for the Phase 2a of the study will initially use data management listings. These Phase 1b data will be combined with data from the Phase 2 of the study and will be presented in the clinical study report.

Continuous variables, including baseline characteristics, will be summarized by reporting the number of observations, mean, standard deviation, median, minimum, and maximum.

Categorical/discrete variables will be summarized using frequency tables showing the number and percentage of patients within a category. Time-to-event data will be summarized using the Kaplan-Meier method.

Unless indicated otherwise, summary statistics will be reported for observed data only. Missing data will not be imputed. If a baseline value is missing, no change from baseline will be calculated. Baseline is defined as the last available observation prior to the first administration of study drug on C1D1.

The handling of missing data will be specified in the SAP along with the methods used for reporting the endpoints.

Statistical analyses will be carried out by IQVIA Biotech using SAS Version 9.4 or higher. Any deviations from the SAP will be reported in the clinical study report.

7.1. Analysis Populations

The modified intent-to-treat (mITT) analysis population will consist of patients enrolled in the Phase 2a and the Phase 2b who meet the eligibility criteria and receive at least 1 dose of BXCL701 and PEMBRO.

In Phase 2a, the response evaluable patient population will consist of patients enrolled who have completed at least 2 cycles of treatment with combined BXCL701 and PEMBRO, with at least 1 post-baseline response assessment made by the investigator(s). Patients who were treated and died before completing 2 cycles and/or having at least 1 post-baseline tumor assessment will also be included in this population.

In Phase 2b, the response evaluable patient population will consist of patients enrolled who have completed at least two cycles of treatment and have had at least one post-baseline tumor assessment which is consistent with RECIST 1.1 criteria. Patients who were treated and died before completing 2 cycles and/or having at least 1 post-baseline tumor assessment will also be included in this population.

The safety population will consist of all patients who receive any dose of BXCL701 or PEMBRO, during any phase of the study.

The pharmacodynamic analysis population will consist of all patients who receive any dose of BXCL701 and PEMBRO and have cytokine levels measured at least once.

The pharmacokinetics population will include all patients who receive at least 1 dose of BXCL701 and have at least 1 quantifiable BXCL701 plasma concentration at a scheduled pharmacokinetics time point post-dose.

7.2. Analysis of Demographics and Baseline Characteristics

Demographics and baseline disease characteristics will be summarized and listed for the safety analysis population. If the number of patients in the safety analysis population differs substantively from the number of patients in the response evaluable or mITT analysis population, demographics and baseline characteristics for these analysis populations may be presented.

7.3. Efficacy Data Analysis

7.3.1. Primary Efficacy Parameters

The primary efficacy parameters are defined in Section 5.2.1.

7.3.2. Secondary Efficacy Parameters

The secondary efficacy parameters are defined in Section 5.2.2.

7.3.2.1. Rate of Objective Response

Objective response rate is defined as the number of patients with a CR or PR among patients with evaluable lesions by RECIST 1.1. Response will be determined by RECIST 1.1 criteria.

7.3.2.2. Duration of Response

Duration of response is defined as the time interval measured in days between the first date when the criteria for objective response are met and the first date on which objective progression is documented or death from any cause, whichever occurs first. Patients who do not experience PD during the treatment and follow-up period, and who do not die during the treatment period, will have their event time censored on the last study date that objective tumor assessments verified lack of PD. One day will be added to each calculation to account for the designation of the first day of treatment as Study Day 1. Patients who achieve a PR and then a CR will have times calculated using the date of the PR.

7.3.2.3. Radiographic Progression-Free Survival

Radiographic PFS is defined as the time from the date of initiation of protocol therapy to the date measurement criteria are first met for PD by RECIST 1.1/PCWG3 criteria or death from any cause, whichever occurs first.

Patients lacking an evaluation of tumor response will have their event time censored on Day 1. Patients not experiencing PD during the treatment and extended disease-assessment period, and who do not die during the treatment period, will have their event time censored on the last date that objective tumor assessments verified lack of PD. A patient's data will be censored at the point he receives new cancer therapy in the absence of documented PD. One day will be added to each calculation to account for the designation of the first day of treatment as Study Day 1.

7.3.2.4. PSA Progression-Free Survival

The PSA PFS is defined as the time from the date of initiation of protocol therapy to the date measurement criteria are first met for PSA progression by PCWG3 criteria or death from any cause, whichever occurs first. Patients who have not met definitive criteria for progression will be censored at the latest date of assessment.

7.3.2.5. Overall Survival

Survival time is the difference in days between the date of death and the first date of study treatment (+1 day). Patients not expiring will have their survival times censored on the last date of known contact on which the patient was documented to be alive. Treated patients lacking data beyond the start of therapy will have their survival times censored on Day 1.

7.3.3. Analysis of the Primary Efficacy Parameter

7.3.3.1. Phase 2a

The Stage 1 analysis will be performed for Cohort A and Cohort B, separately. In each cohort, when 15 patients have completed approximately 2 cycles of treatment and have 1 postbaseline tumor assessment, the number of patients who meet the composite response criteria of achieving 1 or more the following: 1) objective response by RECIST 1.1 criteria or 2) ≥50% decline from baseline in serum PSA will be evaluated.

Using a minimax 2-stage Simon design, if 2 or fewer out of 15 Stage 1 patients meet at least 1 of the composite response criteria, enrollment will be stopped. This will indicate that data to date are consistent with the null hypothesis that the composite response rate is 15% or less, thereby rejecting the alternative hypothesis that the composite response rate is 35%. If 3 or more out of 15 patients meet at least 1 of the composite response criteria, 13 more patients will be enrolled and treated to proceed to Stage 2, for a total of 28 patients in both stages.

In each Cohort enrolling in Stage 2, when the additional 13 patients enrolled and treated in Stage 2 have completed approximately 2 cycles of treatment, 1 post-baseline assessments of tumor, and PSA, the number of patients who meet at least 1 of the 2 criteria for the composite endpoint will be evaluated. If the total number of patients who meet the composite endpoint in 28 patients in both stages is 4 or less, then data are consistent with the null hypothesis of a composite endpoint rate of 15% or lower with a nominal 0.05 one-sided significance level. If the number of patients who meet the composite endpoint is 5 or more, then the data are consistent with the composite endpoint rate of at least 35%. The composite endpoint rate across 2 stages, and its exact 95% confidence interval (CI), will be calculated as if data are collected in a single stage. This approach that ignores the sequential statistical testing may lead to a biased point estimate of the composite endpoint rate and the CI may not provide the stated coverage probability, but it is generally accepted when the event rate is relatively small.

7.3.3.2. Phase 2b

For a given histologic subtype (SCNC or adenocarcinoma), the purpose of the Phase 2b component is to estimate efficacy outcomes in each treatment group individually, with the BXCL701 monotherapy arm serving as an internal reference group; the two treatment groups will not be formally compared. The overall response rate (ORR) will be estimated for each treatment group along with two-sided 95% confidence intervals. In addition, the two-sided 80% confidence interval for the difference in response rates (Miettinen and Nurminen, 1985) will be calculated to inform proof-of-concept.

The total experience for patients within the mCRPC histologic subtype from the Phase 2a and Phase 2b components will collectively provide greater precision in relation to the efficacy and safety of the combination regimen. A pooled (non-comparative) analysis of the Phase 2a (n = 28) and Phase 2b patients (n = 40) with a given histologic subtype receiving the combination regimen will provide the following precision in the estimation of the ORR (approximately 68 total). The lower bound of the confidence interval will inform whether the pooled response rate is clinically meaningful.

7.3.4. Analysis of Secondary Parameters

The distribution of time-to-event response including rPFS, PSA PFS, DOR, and OS will be estimated by Kaplan-Meier methodology. The medians of these time-to-event efficacy responses, if available, and their two-sided 95% CIs will be reported. In addition, milestone rates at selected time points, together with their 2-sided 95% CI, will be presented.

7.3.5. Analysis of Secondary Endpoints: Cytokine Levels

The analysis of the secondary efficacy endpoints including cytokine levels will be reported for the pharmacodynamic analysis population. Descriptive statistics for levels of cytokines previously shown to be modulated by BXCL701 in human will be reported.

7.4. Analysis of Safety

Demographic (e.g., gender, age, race) and baseline characteristics (e.g., ECOG performance status, height, weight, and prior therapy) will be summarized by BXCL701 dose group and disease cohort using descriptive statistics. Treatment-emergent AEs through 30 days after last dose of study treatment will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) Version 13.1 (or higher) System Organ Class and Preferred Term. To the extent possible, AE relationship to either BXCL701 or PEMBRO will be identified in patients who receive the combination therapy. The incidences and percentages of patients experiencing each AE preferred term will be summarized with descriptive statistics. Adverse events will also be summarized by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03 (or higher) grade, and by causality (attribution to study treatment). Dose-limiting toxicities, Grade 3 to 4 AEs, SAEs, and AEs resulting in dose modification or treatment discontinuation will be summarized by preferred terms.

Laboratory results will be classified according to NCI CTCAE, Version 4.03 (or higher). Laboratory results not corresponding to an NCI CTCAE term will not be graded. Incidences of laboratory abnormalities will be summarized with descriptive statistics. Graphic displays and shift tables may be provided to illustrate results over time on study. Assessment of cumulative toxicities may be made.

Electrocardiograms, vital signs, and ECOG performance status will be summarized by visits/cycles using descriptive statistics applicable to continuous or categorical measures of these additional safety data. Summaries for the Phase 1b and Phase 2a and 2b will be presented.

Vital signs and physical examination results will be summarized with descriptive statistics.

Safety outcomes will be summarized separately for the Phase 1b component (by dose cohort), Phase 2a (by disease cohort), and Phase 2b histologic subtype (by treatment arm). In addition, safety data will be combined across all patients from who receive at least one dose of the combination regimen of BXCL701+PEMBRO.

7.5. Statistical Power and Sample Size Considerations

7.5.1. Phase 1b

Approximately 6 to 12 patients with mCRPC will be enrolled in the Phase 1b component of the study.

7.5.2. Phase 2a

The sample size is calculated to reflect Simon's 2-stage design for the Phase 2a. In Simon's 2-stage design, an initial number of patients is enrolled and evaluated for stopping for futility; that is, data are tested for consistency with the null hypothesis using a 1-sided test. If the analysis indicates that data are consistent with the null hypothesis, the study will be stopped for futility. Otherwise, the study proceeds to a second stage where an additional number of patients will be enrolled to test if data support either the null or alternative hypothesis. The Simon 2-stage design only considers stopping for futility at Stage 1, and admissible sample sizes that meet the pre-specified power and type 1 error are considered for both study stages.

For each Cohort, a total sample size of 28 patients, 15 patients at Stage 1 and 13 patients at Stage 2, will be treated with combined BXCL701 and PEMBRO in order to detect with 80% power an alternative hypothesis percentage of patients who meet the composite endpoint of 35% versus the null hypothesis that the percentage of 15%, with early stopping for futility at Stage 1, in a 1-sided test with a 0.05 significance level (actual value is 0.0461). Two or fewer patients who meet the composite endpoint at Stage 1 will trigger early stopping. Seven or fewer patients among 28 patients in both stages will lead to rejecting the alternative hypothesis that the composite endpoint rate is at least 35%.

If a given cohort shows preliminary efficacy in Phase 2a, then the Phase 2b portion of the study will evaluate the histologic subtype in a randomized proof-of-concept study. The description that follows is applicable for the subtype(s) warranting further evaluation in the Phase 2b portion.

7.5.3. Phase 2b

For a given histologic subtype (SCNC or adenocarcinoma), the Phase 2b component will randomize a total of 60 patients, 2:1 to receive the Phase 2a combination regimen of BXCL701 + PEMBRO (n = 40) vs. BXCL701 monotherapy (n = 20). The purpose of the Phase 2b component is to estimate efficacy outcomes in each treatment group individually, with the BXCL701 monotherapy arm serving as an internal reference group; the two treatment groups will not be formally compared. A composite response rate of 25-35% in 40 patients treated with BXCL701 + PEMBRO will result in a 31% absolute maximum width of the estimated exact 95% confidence interval (CI). A composite response rate of 5-15% in 20 patients treated with BXCL701 monotherapy arm will result in a 35% absolute maximum width of the estimated exact 95% CI. If the observed composite response rate is 10/40 (25%) in patients treated with BXCL701 + PEMBRO and 2/20 (10%) in patients treated with BXCL701 monotherapy, then the two-sided 80% confidence interval for the difference in response rates[22] would be (0.96, 26.8), ruling out 0.

In addition, the total experience for patients within the mCRPC histologic subtype from the Phase 2a and Phase 2b components will collectively provide greater precision in relation to the efficacy and safety of the combination regimen. A pooled (non-comparative) analysis of the Phase 2a (n = 28) and Phase 2b patients (n = 40) with a given histologic subtype receiving the combination regimen will provide the following precision in the estimation of the composite response rates (n = 68 total). The lower bound of the confidence interval will inform whether the pooled response rate is clinically meaningful. Based on an expected 5-10% response rate among mCRPC patients who receive PEMBRO monotherapy[13] the table below suggests that observing

13 responses (19.1%) will be clinically meaningful, as it will rule out a <10% response rate with 95% confidence.

Response rate BXCL701 + PEMBRO (n = 68)	95% confidence interval[a]
13/68 (19.1%)	(10.5% - 30.5%)
17/68 (25.0%)	(15.3% - 37.0%)
21/68 (30.9%)	(20.2% - 43.3%)
[a]Clopper-Pearson exact method	

7.6. Replacement of Patients

In the Phase 1b, patients who are assigned a patient number and who discontinue treatment before completion of the DLT period without experiencing a DLT will be replaced for DLT assessment purposes.

In the Phase 2a and the Phase 2b, patients who are assigned a patient number and who discontinue treatment for reasons other than Adverse Event or Progressive Disease before receiving at least 2 cycles of BXCL701 may be replaced and will be excluded from the response evaluable patient population. If a patient receives any dose of BXCL701 or PEMBRO and is replaced, all AEs throughout the treatment period and AE follow-up period (Section 5.4) should be reported. The reasons for treatment discontinuation and study discontinuation will also be collected for replaced patients.

8. INVESTIGATOR REQUIREMENTS

8.1. Protocol Adherence

Each investigator must adhere to the protocol as detailed in this document and agree that any intended departures from the protocol must be approved by the sponsor or the sponsor's designee prior to seeking approval from the IRB and/or Independent Ethics Committee (IEC). Each investigator will be responsible for enrolling only those patients who have met protocol eligibility criteria.

8.2. Case Report Forms

All patient data relating to the study will be recorded on eCRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF. The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

8.3. Study Monitoring Requirements

Site visits will be conducted by the sponsor or sponsor's representative to inspect study data, patients' medical records, and eCRFs in accordance with current Food and Drug Administration (FDA) Good Clinical Practice (GCP), the International Council for Harmonisation (ICH) guidelines, and the respective local and national government regulations and guidelines. The

investigator will permit the sponsor and/or authorized representatives of the sponsor, the FDA, and the respective national or local health authorities to inspect his or her facility and records relevant to this study.

8.4. Drug Accountability

Inventory control of all BXCL701 and PEMBRO must be maintained throughout the duration of the study. Any discrepancies that are noted between drug-dispensing records and drug inventory must be reported. Medication-dispensing records are provided to the investigative site. All study medication used during the study must be accounted for on the appropriate form. All unused study medication must be returned by the patient to the site for completion of the drug accountability record. All unused study medication will be disposed of in biohazard containers in accordance with the policies of the institution by site personnel, with appropriate documentation and approval by the sponsor.

8.5. Retention of Records

Records and documents pertaining to the conduct of this study, including screening logs, eCRFs, source documents, consent forms, laboratory test results, and medication inventory records must be retained by the investigator for at least 2 years following marketing approval of BXCL701 or withdrawal of the Investigational New Drug Application (IND). No study records shall be destroyed without prior authorization from the sponsor.

For studies conducted outside the US under a US IND, the investigator must comply with US FDA IND regulations, the ICH guidelines, and with the regulations of the relevant national and local health authorities.

8.6. Study Discontinuation

The sponsor has the right to terminate this study at any time. Reasons for terminating the study may include the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete.
- Investigator does not adhere to the protocol or applicable regulatory guidelines in conducting the study.

9. ETHICAL CONSIDERATIONS

This study will be conducted in accordance with current FDA regulations, GCP, the ICH guidelines, the ethical principles that have their origins in the Declaration of Helsinki, and local ethical and legal requirements.

9.1. Informed Consent

Sample informed consent documents will be provided to each site. No major deviations should be made from the sample informed consent document.

The sponsor or sponsor's representative will review the draft informed consent before it is finalized, and the final IRB/IEC-approved document must be provided to the sponsor for regulatory purposes.

The informed consent document must be signed by the patient or the patient's legal guardian prior to his participation in the study. A signed copy of the informed consent document must be provided to the patient or the patient's legal guardian. If applicable, it will be provided in a certified translation of the local language.

Signed consent forms must remain in each patient's study file and must be available for verification by study monitors at any time.

9.2. Institutional Review Board or Ethics Committee Approval

This protocol, the informed consent document, relevant supporting information, and all types of patient recruitment or advertisement information must be submitted to the sponsor and/or sponsor's designee and IRB/IEC for review and must be approved before the study is initiated. Any amendments to the protocol must also be approved by the IRB/IEC prior to implementing changes in the study. An amendment to remove a life-threatening situation can be implemented by the sponsor prior to obtaining IRB/IEC approval by the site. In such situations, the chairman of the IRB/IEC should be notified immediately, and the amendment forwarded to the IRB/IEC for their consideration.

The investigator is responsible for keeping the IRB/IEC informed of the progress of the study and of any changes made to the protocol as required by the bylaws of the IRB/IEC at least once a year. The investigator must also keep the IRB/IEC informed of any significant AEs.

9.3. Confidentiality

The information obtained during the conduct of this clinical study is confidential, and disclosure to third parties other than those noted below is prohibited. Information obtained during the conduct of this study will be used by the sponsor in connection with the development of the study drug. The study investigator is obliged to provide the sponsor and/or sponsor's designee with complete test results and all data developed in this study. The sponsor may disclose this information to other physicians who are conducting similar studies, the FDA, and other regulatory authorities as required by local, state, or country laws or as deemed necessary by the sponsor. Patient-specific information may be provided to other appropriate medical personnel only with the patient's permission.

To ensure compliance with current federal regulations and the ICH guidelines, data generated by this study must be available for inspection upon request by representatives of the FDA, national and local health authorities, the sponsor and sponsor's representative, and the IRB/IEC for each study site.

If the investigator desires to publish the results (including meeting abstracts) of this study, a copy of the manuscript or abstract will be provided to the sponsor for review and approval at least 30 days prior to the expected date of submission to the intended publisher. Patient names and other identifiers, such as photographs, audio, or videotapes, may not be disclosed in any publication without prior written authorization from the patient. Because this is a multicenter study, publication of partial results by an investigator(s) is prohibited until the results of the entire study

have been published unless such approval is specifically granted in writing to the investigator by the sponsor.

10. LIST OF ABBREVIATIONS

ADT	Androgen deprivation therapy
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AR	Androgen receptor
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration time curve
BID	Twice daily
BP	Blood pressure
BS	Bone scintigraphy
BUN	Blood urea nitrogen
C	Cycle
Ca	Calcium
CI	Confidence interval
Cl	Chloride
CLL	Chronic lymphocytic leukemia
C_{max}	Maximum plasma concentration
CNS	Central nervous system
CR	Complete response
Cr	Creatinine
CRR	Composite response rate
CT	Computed tomography
CRPC	Castration-resistant prostate cancer
CTC	Circulating tumor cell(s)
CTLA-4	Cytotoxic T lymphocyte–associated antigen 4
CYP	Cytochrome P450
D	Day
DKA	Diabetic ketoacidosis
DLT	Dose-limiting toxicity
dMMr	Deficient mismatch repair
DOR	Duration of response
DPP	Dipeptidyl peptidase
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOT	End of Treatment
FAP	Fibroblast activation protein
FDA	Food and Drug Administration

GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
IC_{50}	Half maximal inhibitory concentration
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IL	Interleukin
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
iRECIST	Immune Response Evaluation Criteria in Solid Tumors
IV	Intravenous(ly)
K	Potassium
LDH	Lactate dehydrogenase
LHRH	Luteinizing hormone-releasing hormone
mCRPC	Metastatic castration-resistant prostate cancer
mCSPC	Metastatic castration-sensitive prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Magnesium
mITT	Modified Intent-to-Treat
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MSI	Microsatellite instability
Na	Sodium
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NEPC	Neuroendocrine prostate cancer
NHL	Non-Hodgkin's lymphoma
NSCLC	Non-small cell lung cancer
OS	Overall survival
PCWG3	Prostate Cancer Working Group 3
PD	Progressive disease/disease progression
PD-1	Programmed cell death 1
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PEMBRO	Pembrolizumab
PFS	Progression-free survival
PI	Principal Investigator
PR	Partial response
PSA	Prostate specific antigen
QD	Once daily

QTcB	QT interval corrected for heart rate using Bazett's formula
RECIST	Response Evaluation Criteria In Solid Tumors
rPFS	Radiographic progression-free survival
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCNC	Small cell neuroendocrine prostate cancer
SJS	Stevens-Johnson syndrome
TEN	Toxic epidermal necrolysis
T1DM	Type 1 diabetes mellitus
t-SCNC	Treatment-emergent form of small cell neuroendocrine prostate cancer
ULN	Upper limit of normal

11. APPENDIX A: Study Schedule of Assessments

Table 2 Study Schedule of Assessments

	Screening Period	C1 or Crossover C1						C2 or Crossover C2					>C2 or Crossover >C2						EOT	FU
Screening/Cycle (C)/ Day (D):	**D-28 to D-1**	**D1**[c]	**D2**	**D4 (+1)**	**D8**	**D14**	**D15**	**D1**[d]	**D2**	**D8**	**D14**	**D15**	**D1**[d]	**D8**	**D14**	**D15**	**D17**	**D19**	**Visit**[a]	**Visit**[b]
Informed consent	X																			
Inclusion and exclusion criteria	X	X																		
Demographics	X																			
Adverse event assessment	X	X	X	X	X		X	X		X		X	X	X[e]		X[e]			X	X
Concomitant medications	X	X			X		X	X		X		X	X	X[e]		X[e]			X	X
Prostate cancer history and treatment[f]	X																			
Archival tumor collection	X																			
Central pathology review of primary or metastatic prostate cancer tissue[g]	X																			
Imaging and Other																				
Bone scintigraphy	X												X[h]						X[h]	
CT/MRI	X												X[h]						X[h]	
Tumor assessment (RECIST 1.1 and iRECIST measurements required)	X												X[h]						X[h]	
Study Drug Administration																				
BXCL701 administration			Day 1-14					Day 1-14					Day 1-14							
PEMBRO administration[i]		X						X					X							
Clinical Procedures																				
Physical examination	X	X			X		X	X		X		X	X						X	
Medical history/current medical conditions	X																			

Screening/Cycle (C)/ Day (D):	Screening Period	C1 or Crossover C1						C2 or Crossover C2					>C2 or Crossover >C2						EOT	FU
	D-28 to D-1	D1[c]	D2	D4 (+1)	D8	D14	D15	D1[d]	D2	D8	D14	D15	D1[d]	D8	D14	D15	D17	D19	Visit[a]	Visit[b]
ECOG performance status	X	X			X		X	X		X		X	X						X	
Vital signs are during the dosing period (sitting and standing after 5 minutes of rest, BP, HR, body temperature, RR).	X	X	X	X	X	X	X	X			X	X	X						X	
Blood pressure monitoring at home Cycle 1 twice daily, prior to each dose[j].			Daily, prior to each dose																	
Review patient BP log. Staff contacts are through C1D14.[k]			X	X	X	X	X													
Height	X																			
Weight	X	X						X					X						X	
Metastatic tumor biopsy[l]	X																			
ECG[m]	X	X						X					X						X	
Administration of IV fluids[n]		X																		
Clinical Laboratory Tests																				
Hematology (CBC plus differential [5-part or auto-analyzer])	X	X			X		X	X		X		X	X	X[o]		X[o,]			X	
Serum chemistry[p]	X	X			X		X	X		X		X	X	X[o]		X[o]			X	
Liver function tests[q]	X	X			X		X	X		X		X	X	X[o]		X[o]			X	
TSH, free T3 and free T4[r]	X							X					X						X	
Serum PSA	X	X						X					X							
Urinalysis	X	X						X					X						X	
Central Laboratory Tests																				
Serum collection for cytokines[s]		X	X	X		X	X	X	X		X	X			X					
Whole blood collection for immune parameters[t]		X				X		X			X									

Screening/Cycle (C)/ Day (D):	Screening Period	C1 or Crossover C1						C2 or Crossover C2					>C2 or Crossover >C2						EOT	FU
	D-28 to D-1	D1[c]	D2	D4 (+1)	D8	D14	D15	D1[d]	D2	D8	D14	D15	D1[d]	D8	D14	D15	D17	D19	Visit[a]	Visit[b]
Cell-Free DNA Analysis Whole Blood Sample [tt]		Sample can be drawn together with any other blood sampling																		
Numeration of CTCs by Veridex assay[v]		X						X					X						X	
PK blood sampling		X[w]		X[w]		X[w]		X[w]			X[w]		X[w]		X[x]	X[x]	X	X		
PK crossover only blood sampling		X[y]				X[y]		X[y]			X[y]		X[y]		X[y]					

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP =blood pressure; BUN = blood urea nitrogen; Ca = calcium; Cl = chloride; Cr = creatinine; CxDx = Cycle (number) Day (number); CBC = complete blood count; CT = computed tomography; CTC = circulating tumor cell; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EOT = End of Treatment; FU = Follow-Up; HR = heart rate; IV = intravenous; K = potassium; LDH = lactate dehydrogenase; Mg = magnesium; MRI = magnetic resonance imaging; MSI = microsatellite instability; Na = sodium; PD = progressive disease; PEMBRO = pembrolizumab; PK = pharmacokinetic; PSA = prostate-specific antigen; QTcB = QT interval corrected for heart rate using Bazett's formula; RR = respiratory rate.

[a] EOT visit(s) are applicable at the End of Monotherapy treatment (prior to crossover), if applicable, and/or after discontinuation of study drugs (within 21 days after the last study drug dose).

[b] Safety Follow-up Visit is to be conducted 30 days (±7 days) after the last dose of study drug and later if drug-related AEs have not resolved at that time. Thereafter, patients without documented PD will be followed every 90 days (±14 days) after the last dose for disease assessments until documentation of PD. After documentation of PD, patients will be followed every 90 days (±14 days) for survival status; such follow-up will likely be conducted by telephone.

[c] If C1D1 occurs <72 hours after Screening, physical examinations, clinical laboratory tests, and ECGs do not need to be repeated.

[d] C2D1 and all subsequent cycles will be 21 days (±3 days) after the previous D1 dose of study drug is administered.

[e] For >Cycle 2, assessment may be performed via telephone if no other reason for clinic visit.

[f] If available, provide data on germline mutations or MSI/dMMr within eCRF.

[g] The results from the central pathology review are not required before enrollment if SCNC or adenocarcinoma without small cell neuroendocrine features confirmed on local pathology review. Central pathology review is optional for the safety lead-in.

[h] Tumor assessment must include cross-sectional imaging (MRI or CT scanning with IV contrast whenever possible) of the chest/abdomen/pelvis plus whole body bone scan. Other body sites (e.g., neck) will be included as clinically indicated. Tumor assessment will be performed at Screening, C4D1 (±7 days), C7D1 (±7 days), C10D1 (±7 days), and D1 (±7 days) of every 3rd cycle thereafter. RECIST 1.1 and iRECIST measurements required.

[i] Either BXCL701 or PEMBRO may be administered first. However, on C1D1, it is recommended that PEMBRO be administered first and that ≥1 hour should elapse before the administration of BXCL701 so that it will be easier to determine the relatedness of any AEs to study drug.

[j] Daily during the dosing period of C1, and during the first week of treatment at 0.3 mg BID (should this occur at a cycle later than C1), the patient will perform at home blood pressure monitoring at least twice daily, once in the morning and once in the late afternoon/evening, prior to dosing. The patient will record blood pressure measurements on a log and will be asked to bring the log with them to every clinic visit during C1 and during the first cycle that their dose is escalated to 0.3 mg BID (should this occur at a cycle later than C1). The patient will be instructed that they must not take their dose if their blood pressure is below 100 mmHg systolic or 50 mmHg diastolic. The patient must report any values below this to study physician immediate.

[k] During the first week of treatment in C1, through D14, the study team will maintain regular daily contact with the patient to remind them of oral hydration guidelines, review the side effects, and review at-home blood pressure measurements.

[l] Tumor biopsy is optional in the Phase 1b and mandatory in the Phase 2. Requirement may be waived if there is no safely accessible lesion OR patient has available archival metastatic tumor tissue.

[m] All ECGs should be performed in triplicate. At screening only QTcB will be measured. To mitigate the risk of spurious readings resulting from anxiety, it is recommended that the ECG be performed prior to blood draws.

[n] Administration of at least 1L of IV fluids is required at C1D1. It is at the investigator's discretion to provide IV hydration during in-person clinic visits beyond C1D1.

[o] C3 and subsequent cycles, D8, and D15: For patients who have not experienced a laboratory abnormality since the start of treatment, or who have had no worsening of baseline laboratory abnormality grade, the clinical laboratory assessments (hematology, serum chemistry, and liver function tests) on D8 and D15 of each cycle are not required. These patients should continue to have clinical laboratory assessments on D1 of each cycle as required. For patients who experience Grade >3 laboratory abnormalities after the start of treatment at Day 1 of any cycle beyond Cycle 3, these patients should continue to have D8 and D15 clinical laboratory assessments until the resolution of the laboratory abnormality.

[p] Serum chemistry will include: Na, K, Cl, bicarbonate, Ca, Mg, phosphate, BUN/Cr, LDH. At Screening and D1 of every cycle, a blood lactic acid and glucose test will be performed. All tests will be performed within 24 hours of dosing or visit.

[q] Liver function tests include aspartate AST, ALT, alkaline phosphatase, total bilirubin, and albumin. All tests will be performed within 24 hours of dosing or visit.

[r] TSH, free T3 and free T4 at screening only. TSH, with reflexive free T3 and free T4 if TSH is abnormal, to be performed every other cycle (2, 4, 6, etc.) and EOT visit. All tests will be performed within 24 hours of dosing or visit.

[s] Serum collection for cytokines will occur pre-dose (recommended within 30 minutes prior to dosing) and 6 (±1 hour) and 24 hours (±4 hours) post-dose on C1D1, C1D14, C2D1, and C2D14 and at C3D14 at pre-dose (recommended within 30 minutes prior to dosing) and 6 hours (± 1 hour) after the morning dose. The D1, 24-hour samples will be collected prior to the D2 morning dose. On C1D4 (+1) only, perform a serum collection for cytokines pre-dose (recommended within 30 minutes prior to dosing).

[t] Whole blood will be collected pre-dose on C1D1, C1D14, C2D1, and C2D14 and assessed for leukocytes by flow cytometry (recommended within 30 minutes prior to dosing).

[u] Whole blood draw for cell-free DNA analysis can occur at any time after informed consent. To minimize venipunctures, the whole blood biopsy sample should be drawn in conjunction with a previously planned blood draw.

[v] Numeration of CTCs will be performed at predose (-2 hours) on C1D1, C2D1, and C4D1, and then on D1 of every third cycle thereafter, and at the EOT visit anytime. Samples need to be shipped to central labs the same day.

[w] PK sample will be collected pre-dose (within 24 hours prior to dose) C1D1, C2D1 and C3D1. Sample will be collected within 30 minutes before morning dose is administered on C1D14 and C2D14 (patient diary to be kept to record the number of doses the patient has taken in the cycle). On C1D4 (+1) only, collect a PK sample pre-dose (recommended within 30 minutes prior to dosing).

[x] C3 only; samples will be collected within 30 minutes (±5 minutes) before the morning dose is administered on D14 and at 2 hours (± 15 minutes), 6 hours (± 30 minutes), and if possible, 10 12 hours* (*optional draw if patient or site cannot accommodate). Additional samples will be collected at these approximate times after the D14 evening dose: 10-14 hours, 60 hours (±24 hours), 108 hours (±24 hours), and 156 hours. The 156-hour sample will be collected within 30 minutes before the C4D1 dose. If C4 is not administered, the sample will be collected 156 hours after the last dose (± 5 hours) (patient diary to be kept to record the number of doses the patient has taken in the cycle).

[y] Predose samples only.

12. APPENDIX B: Detailed Study Procedures by Visit

SCREENING PERIOD (DAY -28 TO DAY -1)

Informed consent will be obtained before any procedures are conducted.

All clinical laboratory tests will be analyzed by the institutional or other local laboratory.

At any time between screening and End-of-Study, a blood sample will be drawn for analysis of cell-free tumor DNA.

Within 28 days prior to the first planned dose of BXCL701, the patient should have the following assessments performed:

- Obtain informed consent.
- Review inclusion and exclusion criteria to determine of the patient is eligible to participate in the study.
- Collect demographic data.
- Assess AEs.
- Document all concomitant medications.
- Record prostate cancer history and treatment.
- Collect archival tumor.
- Conduct central pathology review of primary or metastatic prostate cancer tissue (optional for patients in Phase 1b).
- Assess tumor, which must include cross-sectional imaging (MRI or CT scanning with IV contrast whenever possible) of the chest/abdomen/pelvis plus whole-body bone scan. Other body sites (e.g., neck) will be included as clinically indicated.
- Perform metastatic tumor biopsy (optional for Phase 1b). This may be waived in the absence of a safely accessible lesion OR if patient has available archival metastatic tumor tissue.
- Conduct physical examination (including vital signs [sitting and standing blood pressure, heart rate, respiratory rate, and temperature] and physical measurements [height, weight, and review of systems]).
- Complete medical history.
- Assess ECOG performance status.
- Obtain 12-lead ECG (including assessment of QTcB).
- Perform clinical laboratory assessments:
  - Hematology (complete blood count [CBC] plus differential count);
  - Serum chemistry (Na, K, Cl, bicarbonate, Ca, Mg, phosphate, BUN/Cr, LDH, lactic acid, and glucose test);
  - TSH, free T3 and free T4;
  - Liver function tests (AST, ALT, alkaline phosphatase, total bilirubin, albumin);
  - Serum PSA;
  - Urinalysis.
- Once a patient is deemed eligible for the study, assign sequential patient numbers at each site.

ASSESSMENTS DURING THE TREATMENT PERIOD

Cycle 1 (or Crossover Cycle 1), Day 1

The following tests and procedures will be performed:

- Review inclusion and exclusion criteria to confirm that patient remains eligible to continue in the study.
- Assess AEs.
- Query for concomitant medications.
- Dispense BXCL701 for administration on Cycle 1 Days 1-14.
- Provide patient with at-home blood pressure log and instruct patient on how to perform self-administered blood pressure measurements.
- Administer at least 1 liter of IV fluids.
- Administer PEMBRO.
- Administer BXCL701.
- Conduct physical examination (including vital signs [sitting and standing blood pressure, heart rate, respiratory rate and temperature] and weight).
- Assess ECOG performance status.
- Obtain 12-lead ECG.
- Conduct clinical laboratory assessments:
    - Hematology (CBC plus differential count);
    - Serum chemistry (Na, K, Cl, bicarbonate, Ca, Mg, phosphate, BUN/Cr, LDH, lactic acid, and glucose test);
    - Liver function tests (AST, ALT, alkaline phosphatase, total bilirubin, albumin);
    - Serum PSA;
    - Urinalysis;
    - Serum collection for cytokines pre-dose (recommended within 30 minutes prior to dosing) and 6 (± 1) hours and 24 (± 4) hours post-dose, with the 24-hour post-dose sample collected prior to dosing on Day 2;
    - Collect blood samples for pharmacokinetics pre-dose (within 24 hours prior to initial dose);
    - Whole blood for immune parameters.
- Phase 2a only: Collect blood sample in CellSave preservative tube for CTC numeration (2 hours pre-dose).

Cycle 1(or Crossover Cycle 1), Day 2

- Assess AEs.
- Conduct vital signs (blood pressure, heart rate, respiratory rate, and temperature) prior to dosing.
- Collect patient at-home blood pressure monitoring log and review blood pressure measurements.

Cycle 1(or Crossover Cycle 1), Days 3, 5, 6, 7, 9, 10, 11, 12, 13

- Maintain regular daily contact with patient to remind patient of oral hydration guidelines, review side effects, and review at-home blood pressure measurements.

Cycle 1 (or Crossover Cycle 1), Day 4 (+1 Day)

- Assess AEs.
- Conduct vital signs (blood pressure, heart rate, respiratory rate, and temperature) prior to dosing.
- Collect patient at-home blood pressure monitoring log and review blood pressure measurements.
- Serum collection for cytokines pre-dose (recommended within 30 minutes prior to dosing)
- Collect blood samples for pharmacokinetics pre-dose (recommended within 30 minutes prior to dosing)

Cycle 1 (or Crossover Cycle 1), Day 8

The following tests and procedures will be performed:

- Assess AEs.
- Query for concomitant medications.
- Conduct physical examination (including vital signs [blood pressure, heart rate, respiratory rate, and temperature]) prior to dosing.
- Collect patient at-home blood pressure monitoring log and review blood pressure measurements.
- Assess ECOG performance status.
- Conduct clinical laboratory assessments:
  - Hematology (CBC plus differential count);
  - Serum chemistry (Na, K, Cl, bicarbonate, Ca, Mg, phosphate, BUN/Cr, and LDH);
  - Liver function tests (AST, ALT, alkaline phosphatase, total bilirubin, albumin).

Cycle 1 (or Crossover Cycle 1), Day 14

The following tests and procedures will be performed:

- Collect patient at-home blood pressure monitoring log and review blood pressure measurements.
- Vital signs are during the dosing period (sitting and standing after 5 minutes of rest, BP, HR, body temperature, RR).
- Collect serum for cytokines pre-dose (recommended within 30 minutes prior to dosing) and 6 (±1) hours post morning dose.
- Collect whole blood for immune parameters.
- Collect blood sample for pharmacokinetic analysis within 30 minutes before the morning dose.

Cycle 1 (or Crossover Cycle 1), Day 15

The following tests and procedures will be performed:

- Assess AEs.
- Query for concomitant medications.
- Conduct physical examination (including vital signs [blood pressure, heart rate, respiratory rate, and temperature]).
- Collect patient at-home blood pressure monitoring log and review blood pressure measurements.
- Assess ECOG performance status.

- Conduct clinical laboratory assessments:
  - Hematology (CBC plus differential count);
  - Serum chemistry (Na, K, Cl, bicarbonate, Ca, Mg, phosphate, BUN/Cr, and LDH);
  - Liver function tests (AST, ALT, alkaline phosphatase, total bilirubin, albumin);
  - Serum collection for cytokines 24 (± 4) hours post Day 14 morning dose.

Cycle 2 (or Crossover Cycle 2), Day 1

The following tests and procedures will be performed:

- Assess AEs.
- Query for concomitant medications.
- Dispense BXCL701 for administration on Cycle 2 Days 1-14.
- Administer PEMBRO.
- Administer BXCL701.
- Conduct physical examination (including vital signs [blood pressure, heart rate, respiratory rate and temperature] and weight).
- Assess ECOG performance status.
- Obtain 12-lead ECG.
- Conduct clinical laboratory assessments:
  - Hematology (CBC plus differential count);
  - Serum chemistry (Na, K, Cl, bicarbonate, Ca, Mg, phosphate, BUN/Cr, LDH, lactic acid, and glucose test);
  - TSH, with reflexive free T3 and free T4 if TSH is abnormal;
  - Liver function tests (AST, ALT, alkaline phosphatase, total bilirubin, albumin);
  - Serum PSA;
  - Urinalysis;
  - Serum collection for cytokines pre-dose (recommended within 30 minutes prior to dosing) and 6 (± 1) hours and 24 (± 4) hours post-dose, with the 24-hour post-dose sample collected prior to dosing on Day 2;
  - Collect blood samples for pharmacokinetics pre-dose (within 24 hours prior to morning dose);
  - Whole blood for immune parameters.

Phase 2a only:

- Collect blood sample in CellSave preservative tube for CTC numeration (2 hours pre-dose).

Cycle 2 (or Crossover Cycle 2), Day 8

The following tests and procedures will be performed:

- Assess AEs.
- Query for concomitant medications.
- Conduct physical examination.
- Assess ECOG performance status.
- Conduct clinical laboratory assessments:
  - Hematology (CBC plus differential count);
  - Serum chemistry (Na, K, Cl, bicarbonate, Ca, Mg, phosphate, BUN/Cr, and LDH);

- Liver function tests (AST, ALT, alkaline phosphatase, total bilirubin, albumin).

Cycle 2 (or Crossover Cycle 2), Day 14

The following tests and procedures will be performed:

- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature).
- Collect serum for cytokines pre-dose (recommended within 30 minutes prior to dosing) and 6 (± 1) hours post morning dose.
- Collect whole blood for immune parameters.
- Collect blood sample for pharmacokinetic analysis within 30 minutes before the morning dose.

Cycle 2 (or Crossover Cycle 2), Day 15

The following tests and procedures will be performed:

- Assess AEs.
- Query for concomitant medications.
- Conduct physical examination (including vital signs [blood pressure, heart rate, respiratory rate, and temperature]).
- Assess ECOG performance status.
- Conduct clinical laboratory assessments:
  - Hematology (CBC plus differential count);
  - Serum chemistry (Na, K, Cl, bicarbonate, Ca, Mg, phosphate, BUN/Cr, and LDH);
  - Liver function tests (AST, ALT, alkaline phosphatase, total bilirubin, albumin);
  - Serum collection for cytokines 24 (± 4) hours post Day 14 morning dose.

Cycle 3 or Crossover Cycle 3 and Subsequent Cycles, Day 1

The following tests and procedures will be performed:

- Assess AEs.
- Query for concomitant medications.
- Dispense BXCL701 for administration on Days 1-14 of that cycle.
- Administer PEMBRO.
- Administer BXCL701.
- Conduct physical examination (including vital signs [blood pressure, heart rate, respiratory rate and temperature] and weight).
- Assess ECOG performance status.
- Obtain 12-lead ECG.
- Collect blood sample in CellSave preservative tube for CTC numeration (2 hours pre-dose).
- Conduct clinical laboratory assessments:
  - Hematology (CBC plus differential count).
  - Serum chemistry (Na, K, Cl, bicarbonate, Ca, Mg, phosphate, BUN/Cr, LDH, lactic acid and glucose test).
  - TSH, with reflexive free T3 and free T4 if TSH is abnormal to be performed every other Cycle starting with Cycle 2 (C2, C4, C6, etc.).
  - Liver function tests (AST, ALT, alkaline phosphatase, total bilirubin, albumin).

- Serum PSA.
- Collect blood samples for pharmacokinetics pre-dose (within 24 hours prior to morning dose).
- Phase 2a only: Collect blood sample in CellSave preservative tube for CTC numeration (2 hours pre-dose).
- Urinalysis.

Cycle 3 or Crossover Cycle 3 and Subsequent Cycles, Day 8 and Day 15

- For patients who have not experienced a laboratory abnormality since the start of treatment, or who have had no worsening of baseline laboratory abnormality grade, the clinical laboratory assessments (hematology, serum chemistry, and liver function tests) on Day 8 and Day 15 of each cycle are not required. These patients should continue to have clinical laboratory assessments on Day 1 of each cycle as required. For patients who experience Grade ≥3 laboratory abnormalities after the start of treatment at Day 1 of any cycle beyond Cycle 3, these patients should continue to have Day 8 and Day 15 clinical laboratory assessments until the resolution of the laboratory abnormality.
  - Tumor assessment, which must include cross-sectional imaging (MRI or CT scanning with IV contrast whenever possible) of the chest/abdomen/pelvis plus whole-body bone scan is required. Other body sites (eg, neck) will be included as clinically indicated. Tumor assessment will be performed at C4D1 (± 7 days), C7D1 (± 7 days), C10D1 (± 7 days), and Day 1 (± 7 days) of every third cycle thereafter.

The following tests and procedures will also be performed:

- Assess AEs.
- Query for concomitant medications.
- Conduct clinical laboratory assessments:
  - Hematology (CBC plus differential count);
  - Serum chemistry (Na, K, Cl, bicarbonate, Ca, Mg, phosphate, BUN/Cr, and LDH);
  - Liver function tests (AST, ALT, alkaline phosphatase, total bilirubin, albumin).

Cycle 3 (or Crossover Cycle 3) Only, Days 14 to 21

The following tests and procedures will be performed:

- Collect blood samples for pharmacokinetic analysis within 30 minutes before the morning dose on Day 14 and at 2 hours (± 15 minutes), 6 hours (± 30 minutes), and if possible, 10-12 hours* (*optional draw if patient or site cannot accommodate). Additional samples will be collected at these approximate times after the Day 14 evening dose: 10-14 hours, 60 hours, 108 hours, and 156 hours. The 156-hour sample will be collected within 30 minutes before the C4D1 dose. If C4 is not administered, the sample will be collected 156 hours after the last dose (± 5 hours) (patient diary to be kept to record the number of doses the patient has taken in the cycle).
- Serum samples for cytokines pre-dose (recommended 30 minutes prior to dosing) and 6 hours (± 1 hour) after the morning dose.

Cycle 4 (or Crossover Cycle 4), Day 1, and Every Third Cycle Thereafter

- Phase 2a only: Collect blood sample in CellSave preservative tube for CTC numeration (2 hours pre-dose).

End of Treatment Visit (Prior to Crossover, if Applicable, and/or within 21 Days After the Last Study Drug Dose)

The following tests and procedures will be performed:

- Assess AEs.
- Query for concomitant medications.
- Conduct physical examination (including vital signs [blood pressure, heart rate, respiratory rate, and temperature] and weight).
- Assess ECOG performance status.
- Obtain 12-lead ECG.
- Conduct clinical laboratory assessments:
  - Hematology (CBC plus differential count).
  - Serum chemistry (Na, K, Cl, bicarbonate, Ca, Mg, phosphate, BUN/Cr, and LDH).
  - TSH, with reflexive free T3 and free T4 if TSH is abnormal.
  - Liver function tests (AST, ALT, alkaline phosphatase, total bilirubin, albumin).
  - Urinalysis.
- Tumor assessment, which must include cross-sectional imaging (MRI or CT scanning with IV contrast whenever possible) of the chest/abdomen/pelvis plus whole-body bone scan is required. Other body sites (e.g., neck) will be included as clinically indicated.

Phase 2a only:

- Collect blood sample in CellSave preservative tube for CTC numeration

Follow-Up Visit (Conducted 30 Days [± 7 Days] After the Last Dose of Study Drug and Later if Drug-Related AEs Have Not Yet Resolved.

The following tests and procedures will be performed:

- Assess AEs.
- Query for concomitant medications.

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