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Protocol Title	A Phase 2 Basket Study of BXCL701, a Small Molecule Inhibitor of Dipeptidyl Peptidases (DPP), Administered in Combination with Pembrolizumab in Patients with Advanced Solid Cancers
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TITLE: A Phase 2 Basket Study of BXCL701, a Small Molecule Inhibitor of Dipeptidyl Peptidases (DPP), Administered in Combination with Pembrolizumab in Patients with Advanced Solid Cancers

PROTOCOL NUMBER:

STUDY DRUG: **BXCL701 (Talabostat)**

IND: **146664**

INSTITUTION: The University of Texas MD Anderson Cancer Center

Support provided by: **BioXcel Therapeutics, Inc.**
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SUMMARY

Summary of rationale:

Development of immune checkpoint inhibitors revolutionized treatment of many hard to treat cancers such as melanoma, non-small cell lung cancer, urothelial cancers, kidney cancers, MSI-high colorectal cancers and others. Nevertheless, reported response rates typically range from 13% to 30% for PD1/PD-L1 antibodies and up to 50% for combination of CTLA-4 antibody ipilimumab and PD1 antibody nivolumab.[1-8] In addition, a number of cancers such as MSS colorectal cancer, most of soft tissue sarcoma, prostate cancer, pancreatic cancer and others do not respond to immunotherapy.[9-13] Resistance to immune therapy can be driven by exclusion of CD8+ T-cells and other immune cells or absence of immune cells (immune desert).[14] Activation of innate immunity can activate type I interferon response and increase sensitivity to immune checkpoint inhibitors.[15] We hypothesize that BXCL701 (Talabostat) is a competitive inhibitor of DPPs that can induce innate immune reaction and tumor inflammation, leading to synergistic anticancer activity when combined with the immune checkpoint PD1 targeted antibody pembrolizumab.

Summary of the Study Design:

This is an open-label, single-institution, Phase 2 study to determine the response rate of BXCL701 administered orally and daily, combined with pembrolizumab, in patients with advanced solid cancers. The study will also assess other efficacy parameters, such as progression free survival (PFS), overall survival (OS) and (DOR), as well as the safety the combined treatment. Bayesian optimal phase 2 (BOP2) design will be adopted to monitor efficacy. The study will consist of 2 stages:

1. Lead-in Stage (first 6 patients enrolled) - in which the safety and tolerability of the combination of BXCL701 administered orally daily on Days 1 to 14 of a 21-day cycle plus pembrolizumab 200 mg administered intravenously (IV) on Day 1 every 21 days will be assessed and confirmed in patients with advanced solid cancers. The dose of BXCL701 will be 0.6 mg in two doses (0.3 mg twice a day).
2. Efficacy Stage (BOP2 Stage) - in which patients with advanced solid cancers will be treated with BXCL701 combined with pembrolizumab. Patients enrolled to the Lead-in Stage will be also evaluated in the efficacy stage. Starting from Protocol version 7, new patients enrolled will be administered BXCL701at the starting dose of 0.2 mg orally twice a day for the first 7 days. If well tolerated and in the absence of signs and symptoms of clinically significant hypotension the dose will be escalated to 0.3 mg orally twice a day.

Summary of the Study Objectives

Primary objectives

- To evaluate response rate per RECIST and iRECIST in patients treated in cohort A and in patients treated in cohort B.[19, 20] Tumor measurements will be in QIAC.

- To evaluate dose-limiting toxicities (DLT) in the first 6 patients enrolled to the study.

Secondary objectives

- To evaluate progression-free survival (PFS), overall survival (OS), duration of response, and overall safety and tolerability.

Exploratory objectives

- To evaluate the quantitative and qualitative effects of BXCL701 in combination with pembrolizumab on relevant immune effector cells and cytokines in tumor tissues and blood, respectively.
- To explore the predictive value of baseline PD-L1 tumor expression and tumor mutation burden (TMB) with clinical outcomes
- To evaluate changes in serially collected blood circulating tumor DNA (ctDNA) to assess for tumor response and clonal evolution
- To evaluate pre- and post-treatment PD-L1 PET/CT as a predictive tool for therapeutic efficacy.

1 INTRODUCTION

Development of immune checkpoint inhibitors revolutionized treatment of many hard to treat cancers such as melanoma, non-small cell lung cancer, urothelial cancers, kidney cancers, MSI-high colorectal cancers and others. Nevertheless, reported response rates typically range from 13% to 30% for PD1/PD-L1 antibodies and up to 50% for combination of CTLA-4 antibody ipilimumab and PD1 antibody nivolumab.[1-8] In addition, a number of cancers such as MSS colorectal cancer, most of soft tissue sarcoma, prostate cancer, pancreatic cancer and others do not respond to immunotherapy.[9-13] Resistance to immune therapy can be driven by exclusion of CD8+ T-cells and other immune cells or absence of immune cells (immune desert).[14] Activation of innate immunity can activate type I interferon response and increase sensitivity to immune checkpoint inhibitors.[15] We hypothesize that BXCL701 is a competitive inhibitor of DPPs that can induce innate immune reaction and tumor inflammation, leading to synergistic anticancer activity when combined with the immune checkpoint PD1 targeted antibody pembrolizumab.

1.1 BXCL701 Mechanism of Action

BXCL701 is a competitive inhibitor of DPPs, including DPP4 (CD26), DPP8, and DPP9, members of the postprolyl-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. FAP, as well as DPP8 and 9, are expressed and activated in a wide range of malignancies, especially CRPC, that emerge following treatment of CRPC with second generation anti-androgen (enzalutamide) or cytochrome P450 (CYP)17 (abiraterone) inhibitors. Resistance to androgen ablation therapy also results in the expression of programmed death-ligand 1 (PD-L1), and there is robust correlation between the expression of PD-L1 and the targets of BXCL701, particularly FAP, DPP8 and DPP9. In animal models with fully intact immune systems, BXCL701 and programmed cell death 1 (PD-1) inhibitors resulted in synergistic anti-cancer activity. To date, BXCL701 has been administered to more than 700 individuals, including 585 cancer patients.

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. DPP4/CD26 is a serine protease expressed on a variety of tissues, including T-lymphocytes, endothelial

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 (see Investigators Brochure).[16]

FAP 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. FAP is 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. FAP 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.[17]

DPP8 and DPP9 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.[18] 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 single agent and in combination with chemotherapies. BXCL701 also significantly inhibited the growth of a human osteosarcoma, SK-ES-01, in mouse xenografts (see Investigators Brochure). 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 (see Investigators Brochure). The supporter 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 supporter support the use of BXCL701 as a multimodal DPP inhibitor targeting distinct, yet complimentary, mechanisms in the biology of a cancer.

1.3 Clinical Experience

BXCL701 has been administered to more than 700 human subjects in Phase 1, 2, and 3 clinical trials. Edema and fatigue were the most common adverse events (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 which 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 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 DPP-4 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 maximum plasma concentration ranged from 1 to 2 hours postdose. 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 2 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. 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.

Similar to the AE profile seen in Phase 1 and 2 studies, edema and fatigue were the most common AEs seen in these 2 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. C_{max} and area under the plasma concentration-time curve (AUC) tend to increase proportionally with increasing dose. Co-administration of BXCL701 with a high-fat meal resulted in approximately a 30% decrease in mean plasma levels (C_{max}).

1.4. Pembrolizumab

Pembrolizumab is a humanized monoclonal antibody that binds to the PD-1 receptor with high affinity, thereby blocking the PD-1 receptor-ligand interaction and boosting the immune response against tumor cells. Pembrolizumab was initially approved for the

treatment of refractory melanoma in 2014 (United States Food and Drug Administration [FDA]) and 2015 (European Medicines Agency). Subsequent approvals have included subsets of non-small cell lung cancer, squamous cell carcinoma of the head and neck, classical Hodgkin lymphoma, primary mediastinal large B-cell lymphoma, urothelial carcinoma, gastric cancer, cervical cancer, hepatocellular carcinoma, Merkel cell carcinoma, and any unresectable or metastatic solid tumor with certain genetic anomalies (mismatch repair deficiency or microsatellite instability-high). The safety profile of pembrolizumab includes adverse events (AE) related to increase immune activation and include pneumonitis, hepatitis, nephritis, colitis, and hormonal dysfunction. Full details are available in pembrolizumab Prescribing Information.

2 STUDY OBJECTIVE(S)

2.1 Primary Objectives

- The primary objectives of the study are:
- To evaluate response rate per RECIST and iRECIST in patients treated in cohort A and in patients treated in cohort B.[19, 20] Tumor measurements will be in QIAC.
- To evaluate dose-limiting toxicities (DLT) in the first 6 patients enrolled to the study.

2.2 Secondary Objectives

- The secondary objectives of the study for cohort A and cohort B include:
- To evaluate progression-free survival (PFS)
- To evaluate duration of response
- To evaluate overall survival (OS)
- To evaluate overall safety and tolerability

2.3 Exploratory Objectives

- To evaluate the quantitative and qualitative effects of BXCL701 in combination with pembrolizumab on relevant immune effector cytokines in blood
- To evaluate the quantitative and qualitative effects of BXCL701 in combination with pembrolizumab on various immunological effector cells, including neutrophils, myeloid derived suppressor cells (MDSCs), dendritic cells, cancer associated fibroblast (CAF), T-cells and macrophage density in pre-dose tumor biopsies and when feasible in post-dose tumor tissues.
- To explore the predictive value of baseline PD-L1 tumor expression and tumor mutation burden (TMB) with clinical outcomes
- To evaluate changes in serially collected blood circulating tumor DNA (ctDNA) to assess for tumor response and clonal evolution
- To evaluate pre- and post-treatment PD-L1 PET/CT as a predictive tool for therapeutic efficacy.

3 STUDY DESIGN

This is an open-label, single-institution, Phase 2 study to determine the response rate of BXCL701 administered orally and daily, combined with pembrolizumab, in patients with

advanced solid cancers. The study will also assess other efficacy parameters, such as PFS, OS and DOR, as well as the safety the combined treatment. Bayesian optimal phase 2 (BOP2) design will be adopted to monitor efficacy. The study will consist of 2 stages:

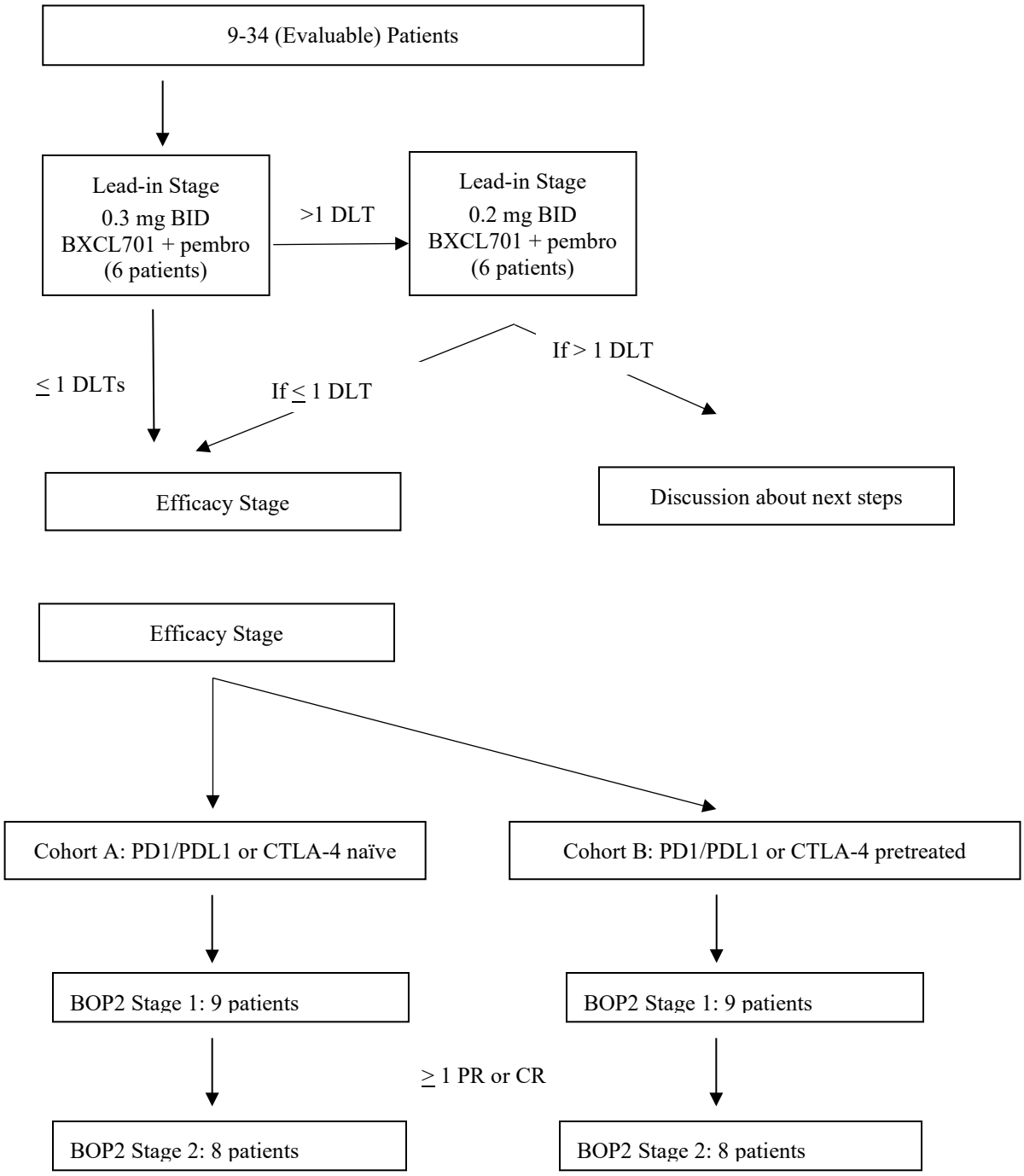
1) Lead-in Stage (first 6 patients enrolled) - in which the safety and tolerability of the combination of BXCL701 administered orally twice a day on Days 1 to 14 of a 21-day cycle plus pembrolizumab 200 mg administered intravenously (IV) on Day 1 every 21 days will be assessed and confirmed in patients with advanced solid cancers. The dose of BXCL701 will be 0.6 mg divided in two doses (0.3 mg twice a day).
2) Efficacy Stage (BOP2-Stage) - in which patients with advanced solid cancers will be treated with BXCL701 combined with pembrolizumab. Patients enrolled to the Lead-in Stage will be also evaluated in the efficacy stage. Starting from Protocol version 7, new patients enrolled will be administered BXCL701 at the starting dose of 0.2 mg orally twice a day for the first 7 days. If well tolerated and in the absence of signs and symptoms of clinically significant hypotension the dose will be escalated to 0.3 mg orally twice a day.

During the Lead-in Stage, patients will be observed for dose-limiting toxicity (DLT) during Cycle 1. Six patients will be treated initially with 0.3 mg BXCL701 twice a day (Days 1 to 14) plus pembrolizumab 200mg:

- If > 1 of the 6 original patients has a DLT in Cycle 1, the dose will be considered above the maximum tolerated dose (MTD) and additional 6 patients will be treated at the 0.4 mg BXCL701 daily Days 1 to 14 dose level.
  - If ≤ 1 of the patients experience a DLT, the Efficacy Stage can commence
  - If > 1 of the patients experience a DLT, a discussion will be held between the investigators and supporters as to how to proceed

The study schema is presented in Figure 1.

Figure 1 Study Schema



DLT = dose-limiting toxicity; pembro = pembrolizumab; PR, partial response; CR, complete response

All safety data from all patients, who received at least one dose of study drug will be included in safety analysis. Unless doses were held because of DLT, a patient must have

received >70% of their BXCL701 in Cycle 1 (i.e., ≥30 of 42 planned doses) with pembrolizumab 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 pembrolizumab) is to be assessed by the investigator using the criteria in the protocol (Section 5.3.1).

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., disease progression) by the Principal Investigator:

- Any Grade 4 laboratory abnormality, regardless of duration.
- Any Grade 3 laboratory abnormalities if associated with clinical symptoms regardless of duration
- Any Grade ≥3 non-hematologic AE, with the exceptions of Grade ≥3 nausea, vomiting, diarrhea, constipation, and fatigue, that resolves to Grade ≤1 within 72 hours with optimal medical management and/or supportive measures.
- 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).
- 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 supporter's medical representatives to be dose-limiting.

Efficacy Stage:

After assessment of the safety and confirmation of the BXCL701/pembrolizumab2 dose schedule to be used in the subsequent stage, the Efficacy Stage will begin. Eligible patients will receive oral BXCL701 daily on Days 1 to 14 of a 21-day cycle plus pembrolizumab 200 mg administered IV on Day 1 every 21 days.

Study Design Features (Both Stages):

In both Lead-in and Efficacy Stages, 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 (Appendix A). 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, if deemed necessary]). 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 progressive disease (PD). Intervals can be shortened to 6 weeks if clinically necessary per treating physician. 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.

Study procedures are listed in Appendix A.

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 IL-6 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/DPP-IV activity to ≤20% of baseline was apparent within 1 hour of dosing, and at doses of ≥0.3 mg, CD26/DPP-IV 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/DPP-IV while also providing significant cytokine (IL-6 and G-CSF) upregulation over baseline.

BioXcel has considered the clinical AE profile of each therapeutic, BXCL701 and pembrolizumab, 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 pembrolizumab include anemia, fatigue, hyperglycemia, hyponatremia, itching, cough, and nausea. A comparison of the safety profiles of BXCL701 and pembrolizumab 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 pembrolizumab is

proposed to be 0.6 mg daily, i.e., the previously identified recommended Phase 2 dose. The dose will be divided into two doses (0.3 mg twice a day) to minimize the risk of hypotension. Based on a review of emerging data from the BXCL701 program, the dosing schedule in the Efficacy Stage 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. BioXcel has evaluated BXCL701 0.4 mg total daily dose with pembrolizumab during Phase 1b of the prostate cancer 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 Bioxcel program is incorporating a one-week lead-in dosing period of 0.2 mg BID to potentially mitigate the effects of cytokine activation, including hypotensive events, which seem to predominantly occur during the first week of treatment in patients starting with 0.3mg BID. 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. Therefore, starting from Protocol version 7, new patients enrolled will be administered BXCL701 at the starting dose of 0.2 mg orally twice a day for the first 7 days. If well tolerated and in the absence of signs and symptoms of clinically significant hypotension the dose will be escalated to 0.3 mg orally twice a day.

4 STUDY POPULATION

Approximately 6 to 12 and 24 to 48 patients who fulfill the eligibility criteria of the protocol will be enrolled during Lead-in and Efficacy Stages of the protocol, respectively. Patients enrolled to the Lead-in Stage will be evaluated and used for the efficacy stage.

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 with a histology or cytology proven solid advanced cancer, which failed or is intolerant of standard therapies known to offer survival benefit unless standard therapies include PD1 or PD-L1 antibodies.
    a. Lead-in stage: patient with advanced cancers meeting the criteria above with or without prior treatment with PD1/PDL1 and/or CTLA-4 targeted therapies. Patients with prior treatment with PD1/PDL1 targeted therapies should be relapsed.
    b. Efficacy stage cohort A: patients with advanced cancers not previously treated with PD1/PDL1 and/or CTLA-4 targeted therapies.
    c. Efficacy stage cohort B: patients with advanced cancers which have relapsed or progressed with PD1/PDL1 and/or CTLA-4 targeted therapies
2. Patient with a life expectancy of more than 3 months, in the opinion of the investigator.
3. Patient has Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.

4. Patient is ≥12 years of age. Patients < 18 years of age have to weigh ≥ 40 kgs.
5. Patients must have measurable disease by RECIST 1.1 and iRECIST. Disease amenable to a biopsy is not mandatory. However, pre and post treatment biopsies (see Appendix A) are mandatory if deemed medically safe and feasible for arms, which advanced to Stage 2 of Efficacy Stage (BOP2).
6. Patient's acute toxic effects of previous anticancer therapy have resolved to ≤Grade 1 except for Grade 2 peripheral neuropathy or any grade of alopecia.
7. Patient has adequate baseline organ function, as demonstrated by the following:
   a. Serum creatinine ≤1.5 times institutional upper limit of normal (ULN) or calculated creatinine clearance >40 mL/min;
   b. Serum albumin ≥2.5 g/dL;
   c. Total bilirubin ≤1.5 × ULN (for patients with known Gilbert syndrome ≤ 3 x ULN);
   d. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 × institutional ULN (patients with hepatic metastases must have AST/ALT ≤5 × ULN).
8. Patient has adequate baseline hematologic function, as demonstrated by the following:
   a. Absolute neutrophil count (ANC) $\geq 1.0 \times 10^9$/L.
   b. Hemoglobin ≥8 g/dL and no red blood cell transfusions during the prior 7 days.
   c. Platelet count $\geq 75 \times 10^9$/L.
9. Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) within 14 days prior to the initiation of treatment and/or postmenopausal women must be amenorrheic for at least 12 months to be considered of non childbearing potential. Women of childbearing potential must agree and commit to the use of 2 highly effective methods of birth control throughout the duration of the study until at least 4 months following the last dose of study drug. Acceptable methods are defined as those that result, alone or in combination, in a low failure rate (ie, less than 1% per year) when used consistently and correctly, such as surgical sterilization, an intrauterine device, or hormonal contraception in combination with a barrier method. It is currently unknown whether BXCL701 or pembrolizumab may reduce the effectiveness of systemically acting hormonal contraceptives; therefore, women using systemically acting hormonal contraceptives should add a barrier method. In certain countries (if permitted by law), WOCBP may agree to abide by heterosexual sexual abstinence during the time of participation in this study.
10. Male patients and their female partners of childbearing potential must agree and commit to use a barrier contraception (eg, condom with spermicidal foam/gel/film/cream/suppository) throughout the duration of the study until at least 60 days 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 4 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 ICF.
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.

4.1.2 Exclusion Criteria

1. Patient cannot swallow oral medication.
2. Patient is on gliptins.
3. Patient has active central nervous system (CNS) metastases not controlled by prior surgery or radiotherapy (patient must be off steroids). Patients with signs or symptoms suggestive of brain metastasis are not eligible unless brain metastases are ruled out by brain MRI/CT.
4. 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.
5. Patient has received treatment with an investigational systemic anticancer agent within 14 days prior to study drug administration.
6. Patient has an additional active malignancy that may confound the assessment of the study endpoints. Patients with the following concomitant neoplastic diagnoses are eligible: non-melanoma skin cancer and carcinoma *in situ* (including transitional cell carcinoma, anal carcinoma, and melanoma *in situ*). Patients with simultaneous cancers, which are not active and do not require treatment may be eligible contingent on discussion with the PI and supporter.
7. 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).
8. Patients with a history of clinically significant hypotension within past 3 months.
9. Patients, who are unable to maintain adequate hydration of $\geq$ 2 liters per day.
10. 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).
11. Patient has uncontrolled intercurrent illness including, but not limited to, uncontrolled infection, disseminated intravascular coagulation, or psychiatric illness/social situations that would limit compliance with study requirements.
12. Patient has known positive status for human immunodeficiency virus active or chronic Hepatitis B or Hepatitis C. Patients with history of hepatitis B or C and undetectable viral load are eligible. Screening is not required.
13. Has a clinically significant upper gastrointestinal obstruction, abnormal physiological function or malabsorption syndrome that may affect the absorption of the study medication.
14. Patient has any medical condition which, in the opinion of the investigator, places the patient at an unacceptably high risk for toxicity.
15. Patient is pregnant or breast-feeding

5 STUDY METHODOLOGY

5.1. Concomitant Medications

5.1.1 Permitted Medications/Therapies

The use of growth factors (e.g., granulocyte-colony stimulating factor [G-CSF]) is allowed as clinically indicated for the treatment of Grade ≥3 cytopenias.

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.

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.

Concurrent radiation is not permitted with the exception of palliative radiation of limited number of isolated solitary lesions.

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. Further, relevant concentrations of BXCL701 did not induce CYP3A4 or CYP1A2. Therefore, there are no prohibited medications based on CYP isoenzymes.

5.2. Efficacy Assessments

Efficacy will be assessed during treatment using the RECIST 1.1 and iRECIST every 9 weeks (every 3 cycles). Intervals can be shortened to 6 weeks (every 2 cycles) if clinically necessary per treating physician. Details on RECIST and iRECIST are described in Appendix B and C. [19, 20] Tumor measurements will be in QIAC.

5.3. Safety Assessments

5.3.1. Non-Serious Adverse Events

An Adverse Event is defined as any untoward medical occurrence in a patient regardless of its causal relationship to study treatment. An AE can be any unfavorable and unintended sign (including any clinically significant abnormal laboratory test result), symptom, or disease temporally associated with the use of the study treatment, whether or not it is considered to be study drug(s) related. Included in this definition are any newly occurring events and any previous condition that has increased in severity or frequency since the administration of study therapy. 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. MOCLIA will be used for eCRF in this study. Department (Investigational Cancer Therapeutics) database team will create the CRF based on protocol requirement and IND monitor will review and approve it once ready.

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 and or pembrolizumab (investigational products, IPs) will be followed to the end of the study or until resolution. AEs will be graded according to the revised NCI CTCAE, Version 5.0, (see http://ctep.cancer.gov/reporting/ctc.html). AEs occurring 30 days after the last dose of IPs do not need to be reported unless the investigator considers the event to be related to IPs.

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 IPs should be reported as AEs. 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.

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 IPs.

The relationship of each AE to each study drug (BXCL701 and/or pembrolizumab) 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.

The investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for all adverse events for subjects enrolled.

Recommended Adverse Event Recording Guidelines

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

5.3.2. Reporting Serious Adverse Events

An adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND supporter, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug or earlier if the participant withdraws consent or starts a new anti-cancer therapy. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND supporter (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the supporter's guidelines, and Institutional Review Board policy.

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

Pharmacokinetic (PK) testing is not planned for this study since PK profiles of both agents are well known

5.6. Pharmacodynamic Assessments

Tumor biopsies (optional for Lead-in Stage and Stage 1 of Efficacy Stage [BOP1]; mandatory for Stage 2 of Efficacy Stage [BOP2]) will be collected at the time points described in Appendix A (Section 12) and the Laboratory Manual. Examples of biomarker analysis of tumor biopsies include immunohistochemistry, RNA sequencing or Nanostring. Whole blood samples (optional for Lead-in Stage and Stage 1 of Efficacy Stage [BOP1]; mandatory for Stage 2 of Efficacy Stage [BOP2]) will be collected at the time points described in Appendix A (Section 12) and Laboratory Manual. Examples of analysis include relevant immune effector cytokines, target engagement, testing of circulating tumor DNA (ctDNA).

5.7. 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 with disease progression per RECIST and/or iRECIST can continue on therapy for clinical benefit if 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

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

5.8. Study Completion

The study will be considered complete when all patients have been followed to disease progression; 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 pembrolizumab may be administered first. However, on Cycle 1 Day 1, it is recommended that pembrolizumab 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 0.1 mg and 0.05 mg tablets for oral administration.

BXCL701 will be administered orally as 0.1 mg and 0.05 mg tablets. BXCL should not be taken on an empty stomach. For a dose of 0.3 mg, patients will take 3 x 0.1 mg tablets and together. Patients will take 0.3 mg of the study drug twice a day, on days 1 to 14 of each cycle, for a total daily dose of 0.6 mg. BXCL701 will be continued until disease progression or unacceptable toxicity. Starting from Protocol version 7, newly enrolled patients will be administered BXCL701 at the starting dose of 0.2 mg (2 x 0.1 mg) orally twice a day. If well tolerated and in the absence of signs and symptoms of clinically significant hypotension the dose will be escalated to 0.3 mg (3 x 0.1 mg) orally twice a day.

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 recommended if not medically contraindicated 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.

On days when pharmacodynamic studies are being performed, BXCL701 should be administered at the study center, and should be administered at (approximately) the same time 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 time of day on each treatment day in the cycle, preferably 0800 hours. If the patient forgets to take study medication the dose will be skipped.

6.2 Dose Adjustments of BXCL701 Secondary to Toxicity

BXCL701 dose modifications (other than recommended in the protocol) within a treatment cycle are discouraged in Cycle 1 unless required by AE and/or DLT. In Cycle ≥2, dose modifications within a treatment cycle will be at the discretion of the investigator. 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 (i.e., the patient forgets to take a dose) may be administered on days subsequent to scheduled doses; any such adjustments should be discussed with the Investigator. Under no circumstances should missed doses be made-up on a day when the patient is already taking a planned dose (i.e., no "doubling-up" to account for missed doses).

Recommendations for BXCL701 dose modifications are:

- Do not administer BXC701 if systolic blood pressure obtained before dosing is less than 100 mmHg
- Grade 2 or higher AEs of edema/peripheral swelling, hypotension, dizziness, and hypovolemia:

  - For Grade 3 AEs, hold/interrupt BXCL701until resolution of these AEs to ≤ Grade 1 or baseline. Thereafter, restart BXCL701 at a dose reduced by 0.2 mg (reduction of 0.1 mg twice day to 0.2 mg twice a day; 1 dose level reduction).
  - For Grade 2 AEs, hold/interrupt BXCL701 until resolution of these AEs to ≤ Grade 1 or baseline. Thereafter, resume at the full dose or at a dose reduced by 0.2 mg (reduction of 0.1 mg twice day to 0.2 mg twice a day; 1 dose level reduction) at the discretion of the investigator.
  - For any Grade 3 or higher edema or Grade 2 edema that has not improved within 7 days, restart BXCL701 at a dose reduced by 0.2 mg (reduction of 0.1 mg twice day to 0.2 mg twice a day; 1 dose level reduction) after resolution of the edema to ≤ Grade 1 or baseline.
- For other Grade 2 or higher AEs deemed related to BXCL701:
  - Hold BXCL701 until resolution of these AEs to ≤ Grade 1 or baseline.
  - For Grade 2 AEs, restart BXCL701 at the full dose or at a dose reduced by 0.2 mg (reduction of 0.1 mg twice day to 0.2 mg twice a day; 1 dose level reduction) at the discretion of the Investigator.
  - For Grade 3 AEs, restart BXCL701 at a dose reduced by 0.2 mg (reduction of 0.1 mg twice day to 0.2 mg twice a day; 1 dose level reduction).
- Once BXCL701 dose has been de-escalated, it may **not be** re-escalated.
- A maximum of 2 dose reductions per participant will be permitted for BXCL701-related AEs, after which the study drug will be permanently discontinued.
- Adverse events deemed related to BXCL701 not recovering to ≤ Grade 1 or baseline within 6 weeks from onset will require permanent discontinuation of BXCL701.
- Discontinue BXCL701 for any life-threatening AE.

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 supporter should be contacted to discuss continuing BXCL701 at the same or reduced 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 and 0.05 mg tablets in high-density polyethylene bottles with desiccant and child-resistant caps. 90 tablets will be provided in each bottle of 0.1 mg and 0.05 mg tablets. 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).

6.5 Pembrolizumab Administration, Dose Modifications and Discontinuation

Pembrolizumab will be prepared, stored, and administered according to the current full Prescribing Information. Pembrolizumab will be obtained from commercial supplies and will be administered 200 mg intravenously over 30 minutes through a 0.2 to 5 micron sterile, nonpyrogenic, low-protein binding online or add-on filter. No other medication will be infused through the infusion line. Infusion will be interrupted and slowed for grade 1 or 2 infusion-related reactions and permanently discontinued for grade 3 or 4 infusion-related reactions. Pembrolizumab will be administered until disease progression, unacceptable toxicity, or withdrawal of consent.

AEs associated with pembrolizumab exposure may be immune-mediated. Immune-related AEs may occur any time after pembrolizumab administration and may affect multiple body systems. Early recognition and treatment are important to reduce complications. Most immune-related AEs are reversible and can be managed with discontinuation of pembrolizumab and initiation of steroids. Refer to the current regional pembrolizumab full Prescribing Information for recommended dose modifications for the management of toxicities (including immune-mediated reactions and infusion-related reactions) considered related to pembrolizumab. Patients who require a dose hold of pembrolizumab of ≥ 42 days will be discontinued from the study.

Pembrolizumab should not be used in conjunction with other immunosuppressive agents other than corticosteroids administered for control of immune reactions considered related to pembrolizumab. Refer to the current regional pembrolizumab full Prescribing Information for further details.

7 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

This is a phase 2, single center, basket study of oral BXCL701 daily on days 1-14 in combination with intravenous PD1/PDL1 antibody on day1 of 21-day cycle in subjects with advanced and refractory malignancies. Lead-in cohort will enroll 6 patients. Only the 6 patients treated at the selected dose during safety lead-in will be assigned to Cohort A or B as appropriate. That is, if there is a dose de-escalation during safety lead-in, then the 6 patients treated at the higher dose will not be assigned to the phase II cohorts. Cohorts A and B will enroll 9 to 17 patients. Response assessments with CT and/or MRI will be done every 9 weeks (3 cycles) following RECIST and iRECIST criteria.[19, 20] Intervals can be shortened to 6 weeks (2 cycles) if clinically necessary per treating physician.

The study will follow the BOP2 design with the following operating characteristics.

Power: 0.80

Type I error: 0.05

P0: 0.05

P1: 0.25

Each cohort will enroll 9 patients. If there is no complete (CR) or partial response (PR) in the first 9 patients the enrolment to that cohort will stop. If there $\geq$ 1 PR or CR in the first 9 patients the enrollment will continue to enroll total of 17 patients. PR or CR does not require confirmation. The treatment will be considered promising for further exploration if $\geq$ 3 CRs or PRs are observed in 17 patients. The expected **Sample Size** will range from 9 (if terminated after safety lead in) to 34 patients. Accounted for ~ 20% of patients not being evaluable for efficacy, the actual number of patients to be recruited for the trial will range from 11 to 42.

Operating characteristics:

Scenarios (PA, PB)	Pr(reject H0 for cohort A)	Pr(reject H0 for cohort B)	Average sample size for cohort A	Average sample size for cohort B
(0.05,0.05)	0.046	0.046	12.0	12.0
(0.05,0.25)	0.046	0.813	12.0	16.4
(0.25,0.25)	0.813	0.813	16.4	16.4
(0.05,0.15)	0.046	0.455	12.0	15.1
(0.15,0.15)	0.455	0.455	15.1	15.1
(0.15,0.25)	0.455	0.813	15.1	16.4

Note: PA is the response rate for cohort A, PB is the response rate for cohort B.

The Investigator is responsible for completing toxicity/efficacy summary reports and submitting them to the IND office Medical Affairs and Safety Group for review. These should be submitted as follows:

- Lead-In Stage:

After the first 6 evaluable patients, complete cycle 1 of study treatment. IND Office approval must be obtained prior to advancing to the efficacy stage.

- Efficacy Stage:

After the first 9 evaluable patients per cohort, complete 9 weeks of study treatment, and after a total of 17 patients per cohort have completed 9 weeks of study treatment. A copy of the cohort summary should be placed in the Investigator's Regulatory Binder under "sponsor correspondence".

Toxicity monitoring is also performed in this stage. If the empirical DLT rate > 33%, we will suspend accrual for safety and discussions for the next step will be made.

7.1 Safety Analyses

All patients in the safety population will be included in the final summaries and listings of safety data for the lead-in patients. Summaries of AEs and other safety parameters will be provided as appropriate. Emphasis in the analysis of AEs will be placed on those that are treatment-emergent through 30 days after last dose of BXCL701 with pembrolizumab

Frequencies of patients experiencing at least 1 AE will be displayed by body system and preferred term according to Medical Dictionary for Regulatory Activities (MedDRA) terminology. Detailed information collected for each AE will include: a description of the event, duration, whether the AE was serious, nature of the event (single episode versus multiple episode), intensity (i.e., NCI CTCAE version 5 grade), relationship to study drug, action taken, clinical outcome, and whether the AE resulted in surgery or alternate procedures. Intensity (severity) of the AEs will be graded according the NCI CTCAE. The latest version of MedDRA and NCI CTCAE will be used.

Summary tables will be prepared to show the number of patients reporting AEs, the frequency of patient reports, and corresponding percentages. Percentages will be calculated using the number of patients in the safety population as the denominator. Within each table, the AEs will be categorized by MedDRA body system and preferred term. Additional subcategories will be based on event intensity and relationship to study drug. AE data will be presented across all cycles and for each cycle. The denominator for each cycle is those patients available at the start of the cycle who received a dose of BXCL701 for that cycle.

To the extent possible, AE relationship to either BXCL701 or pembrolizumab will be identified.

Individual patient listings will be prepared for all AE data.

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 Lead-in and Efficacy Stages will be presented.

7.2 Clinical Laboratory Analyses

All clinical laboratory values will be listed individually and tabulated in a manner to identify safety concerns on a per-patient basis. Listing tables will be prepared for each laboratory measure and will be structured to permit review of the patient data as they progress on treatment. The tables will list the cycle of treatment, BXCL701 dose for Lead-in data, and the associated NCI CTCAE grade. Descriptive summary statistics will be generated per laboratory parameter.

Summary tables will be prepared to examine the distribution of these toxicities per cycle.

Graphic displays and shift tables may be provided to illustrate results over time on study. Assessment of cumulative toxicities may be made.

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 Principal Investigator

or her/his designee prior to seeking approval from the IRB. Each investigator will be responsible for enrolling only those patients who have met protocol eligibility criteria.

8.2 Study Monitoring Requirements

Site visits will be conducted by the sponsor or sponsor's representative to inspect study data, patients' medical records, and other documents in accordance with current Food and Drug Administration (FDA) Good Clinical Practices (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.

8.3 Drug Accountability

Inventory control of all BXCL701 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 their 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.

8.4 Retention of Records

Records and documents pertaining to the conduct of this study, including screening logs, source documents, consent forms, laboratory test results, medication inventory records and other documents must be retained according to the local standard operating procedures and institutional and/or IRB policies.

8.5 Study Discontinuation

A discontinuation occurs when an enrolled patient ceases participation in the study, regardless of the circumstances, prior to completion of the protocol. The investigator must determine the primary reason for discontinuation. The investigator or study coordinator must notify the supporting company immediately when a subject/patient has been discontinued/ withdrawn due to an adverse experience (telephone or FAX). When a subject/patient discontinues/withdraws prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation.

8.5.1 Discontinuation/Withdrawal Criteria

- A patient may be withdrawn by the investigator or the supporting company if he/she violates the study plan or for administrative and/or other safety reasons.
- The patient withdraws consent at any time after agent administration. Every effort will be made to determine why any subject withdraws from the study prematurely.

- The patient is lost to follow-up. A genuine effort must be made to determine the reason(s) why a patient fails to return for the necessary visits. If the subject is unreachable by telephone, a registered letter, at the minimum, should be sent requesting him/her to contact the clinic.
- Disease progression. RECIST 1.1 and iRECIST will be used for assessment of tumor response for the purposes of managing patients on protocol treatment and decision making for discontinuation of study therapy due to disease progression. Response assessments with CT and/or MRI will be done every 9 weeks (3 cycles) following RECIST and iRECIST criteria (intervals can be shortened to 6 weeks if clinically necessary per treating physician). Patients with disease progression per RECIST and/or iRECIST can continue on therapy for clinical benefit if deemed appropriate by the investigator.
- The patient starts a new anti-cancer therapy
- There is a need for any treatment not allowed by the protocol
- Any life-threatening AE.

Any adverse experiences that are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 5.3 Safety Assessments.
Patients who discontinue study treatment who have not shown disease progression and have not withdrawn consent will continue to be followed for disease progression and survival.

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.

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
$AUC_{0\text{-last}}$	Area under the plasma concentration time curve for the last measurable concentration
BID	Twice daily
BS	Bone scintigraphy
BUN	Blood urea nitrogen
C	Cycle
Ca	Calcium
CAF	Cancer associated fibroblast
CI	Confidence interval
Cl	Chloride
CLL	Chronic lymphocytic leukemia
C_{max}	Maximum plasma concentration
CNS	Central nervous system
CR	Complete response
Cr	Creatinine
CRPC	Castration-resistant prostate cancer
CT	Computed tomography
CTC	Circulating tumor cells
ctDNA	Circulating tumor DNA
CTLA-4	Cytotoxic T-lymphocyte–associated antigen 4
CYP	Cytochrome P450
D	Day
DKA	Diabetic ketoacidosis
DLT	Dose-limiting toxicity
DOR	Duration of response
DPP	Dipeptidyl peptidase
DSRC	Data Safety Review Committee
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
ITT	Intent-to-Treat
IV	Intravenous
K	Potassium
LDH	Lactate dehydrogenase
LHRH	Luteinizing hormone-releasing hormone
MDSC	Myeloid derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Magnesium
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
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
PD-1	Programmed cell death **1**
PD-L1	Programmed death-ligand 1
PD-L2	Programmed death-ligand 2
PFS	Progression-free survival
PR	Partial response
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

SJS	Stevens-Johnson syndrome
TEN	Toxic epidermal necrolysis
T1DM	Type 1 diabetes mellitus
t_{max}	Time of maximum observed concentration
ULN	Upper limit of normal
US	United States

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12 APPENDIX A: STUDY SCHEDULE OF ASSESSMENTS

	Screen Period		Cycle 1					Cycle 2					>Cycle 2				EOT Visit[a]	FU Visit[b]
Screen/Cycle Day (D):	**D-28 to D-1**	**D1[i]**	**D2**	**D5[t]**	**D8[r]**	**D14**	**D15[r]**	**D1[c]**	**D2**	**D8[r]**	**D14**	**D15[r]**	**D1[c]**	**D8**	**D14**	**D15**		
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	X
Concomitant Medications	X	X	X	X	X		X	X		X		X	X				X	X
cancer treatment history	X																	
Archival tumor collection[l]	X																	
Imaging and Other																		
CT/MRI	X												X[d]				X[d]	
Tumor assessment	X												X[d]				X[d]	
Study Drug Administration																		
BXCL701 administration			Day 1-14					Day 1-14					Day 1-14					
Ambulatory monitoring of blood pressure before each dose of BXCL701			Day 1-14					Day 1-14					Day 1-14					
Oral hydration monitoring			Day 1-14					Day 1-14					Day 1-14					
Daily safety telephone calls			Day 3-4, Day 6-14															
Pembrolizumab administration[j]		X						X					X					
Clinical Procedures																		
Physical examination	X	X	X	X	X		X	X		X		X	X				X	
Medical history/current medical conditions	X	X	X	X	X		X	X		X		X	X				X	
ECOG performance status	X	X	X	X	X		X	X		X		X	X				X	

	Screen Period		Cycle 1					Cycle 2					>Cycle 2				EOT Visit[a]	FU Visit[b]
Screen/Cycle Day (D):	**D-28 to D-1**	**D1[i]**	**D2**	**D5[t]**	**D8[r]**	**D14**	**D15[r]**	**D1[c]**	**D2**	**D8[r]**	**D14**	**D15[r]**	**D1[c]**	**D8**	**D14**	**D15**		
Vital signs (BP, HR, body temperature, RR, O2 saturation)	X	X	X	X	X		X	X		X		X	X				X	
Height	X	X	X	X	X		X	X		X		X	X				X	
Weight	X	X	X	X	X		X	X		X		X	X				X	
Clinical Laboratory Tests[q]																		
Hematology (CBC plus differential [5-part or auto-analyzer])	X	X			X		X	X		X		X	X	X[v]		X[v]	X	
Serum chemistry[e]	X	X			X		X	X		X		X	X	X[v]		X[v]	X	
Liver function tests[f]	X	X			X		X	X		X		X	X	X[v]		X[v]	X	
T3, FT4, TSH	X[u]												X[u]				X[u]	
Cytokine-12 panel		X	X	X														
Urinalysis	X	X						X					X				X	
Serum collection[g]		X	X			X	X	X	X			X						
Whole blood collection for immune parameters[k]		X					X	X				X					X	
Tumor biopsies[m]	X[m]									X[m]							X[m]	
Blood collection for ctDNA[s]		X[h]	X[h]		X[h]		X	X[h]					X[h]				X	
Pregnancy test	X[n]	X[o,p]						X[o]					X[o]					

Abbreviations: BP = blood pressure; CxDx = Cycle (number) Day (number); CBC = complete blood count; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EOT = End of Treatment; FU = follow-up; HR = heart rate; MRI = magnetic resonance imaging; RR = respiratory rate.

a. After discontinuation of study drugs, patients will complete an EOT visit within 21 days after the last study drug dose.

b. A 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 disease progression (PD) will be followed every 90 days for disease assessments until documentation of PD. After documentation of PD, patients will be followed every 90 days for survival status; such follow-up will likely be conducted by telephone.
c. Day 1 of Cycle 2 and all subsequent cycles will be 21 days (±3 days) after the previous dose of study drug was administered.
d. Tumor assessment must include cross-sectional imaging (MRI or CT scanning with intravenous contrast whenever possible) of the chest/abdomen/pelvis plus whole-body bone scan. Other body sites (e.g., neck) to be included as clinically indicated. Tumor assessment to be performed at Screening, C4D1 (±7 days), C7D1 (±7 days), C10D1 (±7 days), and Day 1 (±7 days) of every 3rd cycle thereafter and at EOT. Intervals for scans can be shortened to 6 weeks (e.g. C3D1, C5D1 etc.) if clinically necessary per treating physician.
e. Serum chemistry to include: sodium (Na), potassium (K), chloride (Cl), bicarbonate, calcium (Ca), magnesium (Mg), phosphate, blood urea nitrogen (BUN)/creatinine (Cr), and lactate dehydrogenase (LDH).
f. Liver function tests include aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, and albumin.
g. Serum will be collected if feasible predose (within 1 hour ± 30 minutes) and then 6 hours (± 1 hour) and 24 hours (±3 hours) postdose on C1D1. It will be also collected on C1D14 (± 1 days) and C2D1 (± 1 day) with the same daily schedule as C1D1 (pre-dose, 6 and 24 hours post-dose). The C1D1 and C2D1 24-hour samples will be collected prior to the D2 doses. C1D14 24-hour samples will be collected on C1D15. There will not be predose or 6-hour postdose serum collection on C2D14. Instead, there will be only one time 24-hour postdose collection on C2D15. Details about collection and processing are in the Laboratory Manual.
h. Samples should be collected before dosing.
i. If Cycle 1 Day 1 occurs <72 hours after Screening, physical examinations and clinical laboratory tests do not need to be repeated.
j. Either BXCL701 or pembrolizumab may be administered first. However, on Cycle 1 Day 1, it is recommended that pembrolizumab will 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. It is s recommended to administer at least 1L of IV fluids if not medically contraindicated 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.
k. Whole blood will be collected on C1D1, C1D15 (±1 day), C2D1, C2D15 (±1 day), and at EOT for assessment of leukocytes by flow cytometry and other studies. Details about collection and processing are in the Laboratory Manual.
l. Archival tissue will be collected if available. Details about collection and processing are in the Laboratory Manual.
m. Optional tumor biopsies will be obtained during screening and between Day 8 and Day 14 of cycle 2, and at EOT. Pre and post treatment biopsies will be mandatory if medically feasible in cohorts advancing to BOP2 stage. Details about collection and processing are in the Laboratory Manual.

n. Pregnancy tests will be only for women with child bearing potential. Only whole blood will be collected for the pregnancy test that will be performed in the screening period (D -28 to D -1)
o. Additional pregnancy tests will be performed D1 of each cycle only for women with child bearing potential. Whole blood or urine can be collected for the test.
p. Pregnancy test for the D1 of the 1st cycle can be skipped if the test for the screening period is performed close to the 1st cycle.
q. Laboratory assessment for immune-related toxicities will be added as per patient's toxicity and as needed upon the investigator's discretion.
r. Days 8 and 15 of Cycles 1 and 2 can have a window of ± 2 days. These visits can be also preformed using the telehealth in case of unanticipated events such as COVID-19 pandemics if in agreement with applicable regulations.
s. Details about collection and processing are in the Laboratory Manual.
t. C1D5 visit has a window of -1 day and can happen on C1D4.
u. T3, FT4 and TSH testing will performed at baseline, C4D1 (±7 days), C7D1 (±7 days), C10D1 (±7 days), and Day 1 (±7 days) of every 3rd cycle thereafter and at EOT.
v. Hematology (CBC plus differential [5 part or auto-analyzer]), serum chemistry and liver function tests will not be performed on Days 8 and 15 after Cycle 4 (at Cycle 5 and beyond)

13 APPENDIX B: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) VERSION 1.1

Adopted from the bibliographic reference [20].

13.1 Measurability of tumor at baseline

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows. Measurable lesions must be accurately measured in at least 1 dimension (longest diameter in the plane of the measurement to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable lesions are all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), as well as non-measurable lesions.

13.2 Response criteria

Response criteria	Evaluation of target lesions
CR	Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm.
PR	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
PD	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of 1 or more new lesions is also considered progression).
SD	Neither sufficient shrinkage from the baseline study to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Abbreviations: CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease.

13.3 Evaluation of best overall response

Time point response: At each protocol specified time point, a response assessment should occur. Table below provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Table: Response in patients with target disease

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Inevaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease.

13.4 Duration of response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.
Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

14 APPENDIX C: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS FOR IMMUNE-BASED THERAPIES (iRECIST)

Adopted from the bibliographic reference [19].

14.1 Comparison of response evaluation criteria in solid tumors (RECIST) 1.1 and modified response evaluation criteria in solid tumors for immune-based therapies (iRECIST)

	RECIST 1.1.	iRECIST
Definitions of measurable and non-measurable disease; numbers and site of target disease	Measurable lesions are ≥10 mm in diameter (≥15 mm for nodal lesions); maximum of 5 lesions (2 per organ); all other disease is considered non-target (must be ≥10 mm in short axis for nodal disease)	No change from RECIST 1.1; however, new lesions are assessed as per RECIST 1.1 but are recorded separately on the case report form (but not included in the sum of lesions for target lesions identified at baseline)
Complete response, partial response, or stable disease	Cannot have met criteria for progression before complete response, partial response, or stable disease	Can have had iUPD (one or more instances), but not iCPD, before iCR, iPR, or iSD
Confirmation of complete response or partial response	Only required for non-randomized trials	As per RECIST 1.1
Confirmation of stable disease	Not required	As per RECIST 1.1
New lesions	Result in progression; recorded but not measured	Results in iUPD but iCPD is only assigned on the basis of this category if at next assessment additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions when none have previously been recorded, can also confirm iCPD

Independent blinded review and central collection of scans	Recommended in some circumstances - eg, in some trials with progression-based endpoints planned for marketing approval	Collection of scans (but not independent review) recommended for all trials
Confirmation of progression	Not required (unless equivocal)	Required
Consideration of clinical status	Not included in assessment	Clinical stability is considered when deciding whether treatment is continued after iUPD

"i" indicated immune responses assigned using iRECIST.
Abbreviations: iCPD=confirmed progression; iCR=complete response; iPR=partial response; iSD=stable disease; iUPD=unconfirmed progression; RECIST=Response Evaluation Criteria in Solid Tumors

14.2 Assessment of timepoint response using modified response evaluation criteria in solid tumors for immune-based therapies (iRECIST)

Target lesions	Non-target lesions	New lesions	Timepoint response with no previous iUPD in any category	Timepoint response with previous iUPD in any category[a]
iCR	iCR	No	iCR	iCR
iCR	Non-iCR/non-iUPD	No	iPR	iPR
iPR	Non-iCR/non-iUPD	No	iPR	iPR
iSD	Non-iCR/non-iUPD	No	iSD	iSD
iUPD with no change, or with a decrease from last timepoint	iUPD with no change, or decrease from last timepoint	Yes	Not applicable	New lesions confirm iCPD if new lesions were previously identified and they have increased in size (≥5 mm in sum of measures for new lesion target or any increase for new lesion non-target) or number; if no change is seen in new lesions (size or number) from last timepoint, assignment remains iUPD
iSD, iPR, iCR	iUPD	No	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further

				increase in the size of non-target disease (does not need to meet RECIST 1.1 criteria for unequivocal progression)
iUPD	Non-iCR/non-iUPD, or iCR	No	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in sum of measures ≥5 mm; otherwise, assignment remains iUPD
iUPD	iUPD	no	iUPD	Remains iUPD unless iCPD is confirmed based on a further increase in previously identified target lesion iUPD in sum of measures ≥5 mm or non-target lesion iUPD (previous assessment need not have shown unequivocal progression)
iUPD	iUPD	Yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in previously identified target lesion iUPD sum of measures ≥5 mm, previously identified non-target lesion iUPD (does not need to be unequivocal), or an increase in the size or number of new lesions previously identified
Non-iUPD Or progression	Non-iUPD or progression	Yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of an increase in the size or number of new lesions previously identified

[a] Previously identified in assessment immediately before this timepoint.
Abbreviations: iCPD=confirmed progression; iCR=complete response; iPR=partial response; iSD=stable disease; iUPD=unconfirmed progression; non-iCR/non-iUPD=criteria for neither CR nor PD have been met; RECIST=Response Evaluation Criteria in Solid Tumors.