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

Statistical Analysis Plan

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ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AUC	Area Under Curve
CI	Confidence Interval
C_{max}	Maximum Observed Concentration
C_{min}	Minimal Observed Concentration
CR	Complete Response
CRR	Composite Response Rate
CTC	Circulating Tumor Cell
DLT	Dose-Limiting Toxicity
DOR	Duration of Response
DPPs	Dipeptidyl Peptidases
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
IL	Interleukin
iRECIST	Immune Response Evaluation Criteria in Solid Tumors
IV	Intravenously
mCRPC	Metastatic Castration-Resistant Prostate Cancer
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NEPC	Small Cell Neuroendocrine Prostate Cancer
ORR	Objective Response Rate
OS	Overall Survival
PCWG3	Prostate Cancer Working Group 3
PD	Progressive Disease
PEMBRO	Pembrolizumab
PFS	Progression Free Survival
PK	Pharmacokinetic
PR	Partial Response
PSA	Prostate-Specific Antigen
PSA PFS	Prostate-Specific Antigen Progression-Free Survival
PT	Preferred Term
QD	Once Daily
RECIST	Response Evaluation Criteria In Solid Tumors
rPFS	Radiographic Progression-Free Survival
SAP	Statistical Analysis Plan

SCNC	Small Cell Neuroendocrine Prostate Cancer
SD	Stable Disease
SOC	System Organ Class
StD	Standard Deviation
$t_{1/2}$	The Apparent Terminal Elimination Half-Life
TEAE	Treatment Emergent Adverse Event
t_{last}	Time to Last Measurable Plasma Concentration
t_{max}	Time to Maximum Plasma Concentration
TNM	Tumor Classification Index (Tumor, Nodes, Metastasis)
UTA	Unable to Assess
$V_{d/F}$	Volume of Distribution
V_{ss}	Volume of Distribution at Steady State
WHO	World Health Organization

I. Introduction

A. Background

Prostate cancer is the most common malignancy in men and the second leading cause of cancer-related deaths[1]. 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 and prostate-specific antigen (PSA). An unmet medical need remains for patients in the metastatic Castration-Resistant Prostate Cancer (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 androgen receptor or PSA. SCNC occurs de novo or as a recurrent tumor in patients who have received hormonal therapy for prostatic adenocarcinoma[2,3]. Such tumors do not respond to hormonal therapy targeting the androgen receptor signaling pathway, and so accurate diagnosis of SCNC is important[4]. Treatment of SCNC typically requires early combination chemotherapy and locoregional control of bulky tumor deposits, including untreated or recurrent primaries[5]. BXCL701 is a competitive inhibitor of dipeptidyl peptidases (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 immune-stimulation 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 been administered to more than 700 human patients in Phase 1, 2, and 3 clinical trials. It was generally well tolerated, and edema and fatigue were the most common adverse events (AEs) seen in these trials.

The protocol for Study BXCL701-201 describes the general approach to analysis of data from the study. This analysis plan describes additional detail needed to complete such an analysis.

B. Protocol and Amendment History

This Statistical Analysis Plan (SAP) is based on Amendment 7 of Protocol BXCL701-201 dated 11August2021.

This SAP will govern the analysis of data from this study. The plan may be modified until the clinical database lock. Any deviations from the analysis plan, including any after the time of database lock, will be documented as such in the study report.

II. Protocol Objectives

The purpose of the study is to assess the safety and efficacy of BXCL701 monotherapy in combination with pembrolizumab in patients with 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, patient 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 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.

A. Primary Objectives

Phase 2a primary objectives:

- To estimate the composite response rates (CRR) of the combination of BXCL701 + pembrolizumab (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 objectives:

- 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

B. Secondary Objectives

The Phase 2a secondary objectives 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
- To estimate the median duration of PSA_{50} response (PSA DOR) of the combination of BXCL701 and PEMBRO in Cohort A and B
- To estimate the median duration of Stable Disease of the combination of BXCL701 and PEMBRO in Cohort A and B

The Phase 2b secondary objectives are:

- To estimate the CRR, OS, duration of response, rPFS, PSA DOR, duration of SD 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

C. 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

III. Study Endpoints

A. Primary

In Phase 2a, the primary endpoint is the composite response 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
- Greater than 50% PSA decline from baseline

In Phase 2b, the primary endpoint is objective response by RECIST 1.1 criteria.

B. Secondary

In Phase 2a, the secondary endpoints are:

- Radiographic progression-free survival (rPFS)
- PSA progression-free survival (PSA PFS)
- Overall survival (OS)
- DOR
- Safety of BXCL701 in combination with PEMBRO
- Pharmacokinetics of BXCL701
- Pharmacodynamic profile of the combination of BXCL701 and PEMBRO
- PSA_{50} Duration of Response (PSA DOR)

Duration of stable disease by RECIST 1.1In Phase 2b, the secondary endpoints are:

- Composite response
- Radiographic progression-free survival (rPFS)
- PSA progression-free survival (PSA PFS)

- Overall survival (OS)
- DOR
- PSA_{50} Duration of Response (PSA DOR)
- Duration of stable disease by RECIST 1.1

IV. Study Design

A. Design Overview

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, DOR, PSA DOR and duration of SD, as well as the safety of the combined treatment. The study will consist of three components:

1) 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 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.
2) Phase 2a (Simon's 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 including mixed SCNC.
   - Cohort B: Patients with adenocarcinoma and no evidence of small cell or neuroendocrine features.
3) 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.

B. Study Population

Approximately 6 to 12 evaluable patients with mCRPC will be enrolled in Phase 1b of the study. A total of between 30 and 56 evaluable patients will be enrolled across 2 separate Cohorts in the Efficacy Stage 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. The full list of inclusion/exclusion criteria can be found in Protocol Sections 4.1.1-4.1.2.

C. Sample Size Calculations

- Phase 2a

The sample size is calculated to reflect Simon's 2-stage design for 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's 2-stage design only considers stopping for futility at stage 1, and admissible sample sizes that meet 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 patients who meet the composite endpoint is 15%, with early stopping for futility at stage 1, in a 1-sided test with 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.

- 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 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, 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	

D. Treatment Randomization

Upon the completion of the Phase 2a portion 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.

E. Assessment Schedule

Patients will be requested to attend scheduled visits as defined in Protocol Appendix A. The date at which the patient receives the first dose (Cycle 1 Day 1) will be referred to as the "start date." The acceptable visit window is ±7 days for scheduled tumor assessment visits. Visits that patients make to the clinic outside the visit window are recorded as unscheduled visits.

V. Interventions

A. Clinical Trial Material

The clinical trial material is described in detail in the protocol in Section 6.

BXCL701

BXCL701 will be administered orally as 0.05 mg, 0.1 mg, and 0.2 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 progressive disease (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 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.

Pembrolizumab

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

VI. General Analytical Considerations

A. Data Sources

A web-based Electronic Data Capture system, InForm, will be used for data collection and query handling.

In addition, PK data will be received via electronic data transfers from Northeast Bioanalytical Laboratories LLC for tabulation and listing. CTC data will be sent via electronic data transfer from Cerba to BioXcel. BioXcel will share the CTC data with IQVIA Biotech per request.

B. Definition of Baseline

Study Day 1 is designated as the first day a patient receives BXCL701 and/or PEMBRO. Baseline is defined as the last available observation prior to the first administration of study drug.

Note that for this study there is no study Day 0, so the day immediately prior to study Day 1 is study Day -1. For any events on or after the first dose of study drug, study day is calculated as: event date – date of first administration of study treatment + 1. As such, the first dose date is study Day 1. For any events before the first dose date, study day is calculated as: event date – date of first administration of study treatment. As such, one day before first dose date is study Day -1.

C. Missing Data

Unless stated otherwise, missing data will not be imputed. However, if there are dates missing for AEs or medications, some intermediate steps may be taken for the determination of being treatment emergent or not. Sections below address such procedures for the handling of those dates in the relevant analyses:

<u>Missing or Partial AE or Medication start or stop date</u>:

For partial start-dates:

- If the year is unknown, then the date will not be imputed and will be assigned a missing value
- If the month is unknown, then:
    a. If the year matches the year of the first dose date, then impute the month and day of the first dose date
    b. Otherwise, assign as missing
- If the day is unknown, then:
    a. If the month and year match the month and year of the first dose date, then impute the day of the first dose date
    b. Otherwise, assign as missing

For partial end-dates:

- If the year is unknown, then the date will not be imputed and will be assigned a missing value
- If the month is unknown, then assign as missing
- If the day is unknown, then assign the last day of the month

If the AE start or stop date is still missing after implementing the rules specified above, the following strategy will be used to determine whether AEs with missing start or stop dates are pre-treatment or treatment-emergent:

- If the start date and stop date are both missing, the most conservative approach is taken and the AE is considered to be treatment-emergent
- If the start date is missing but the stop date is not missing and is after the day of study dose administration, then the most conservative approach is taken, and the AE is considered to be treatment-emergent
- If the start date is missing but the stop date is not missing and is on or before the day of study dose and after the date of signed informed consent, then the AE is considered to be pre-treatment (not TEAE)
- If imputed stop date is less than start date, it will be newly imputed to start date+1
- If stop date is less than imputed start date, the start date will be newly imputed to stop date -1

If the toxicity grade is missing, missing grade will be treated as unknown and summarized in AE TLs. If AE relationship with study drug data is missing, 'Related' will be imputed. If AE seriousness is missing, it will be imputed as non-serious AE.

D. Multiple Study Centers

Patients are enrolled without regard for study site balance. Study site is not a stratification factor in phase 2b. Analyses of efficacy data will not be stratified by study site. Summaries of safety data will incorporate study site only if needed to address regulatory requirements or queries.

E. Covariate Adjustment in Primary Analysis

No adjustments for covariates are planned for the primary analysis in this study.

F. Sample Size Reassessment

Not applicable.

G. Interim Analyses or Timing of Analyses

Interim analyses will be performed in Phase 2a Cohort A and Cohort B using two-stage design after 15 patients have completed approximately 6 cycles of treatment and have 2 post-baseline tumor assessments and PSA or CTC measurements, as outlined in section IV.C. If 3 or more responders are observed in stage 1 prior to all 15 patients complete 2 post-baseline tumor assessments, the

study may start enrolling patients in stage 2 upon the scientific review committee's review and approval.

As a result of the interim analysis, enrollment may be stopped early for futility.

No formal statistical analysis is planned for interim analyses.

H. Test Sizes

In Phase 2a, using Simon's 2-stage design, the study will have 80% power to detect an alternative hypothesis percentage of patients who meet the composite endpoint of 35% versus the null hypothesis that the percentage of patients who meet the composite endpoint is 15%, with early stopping for futility at stage 1, in a 1-sided test with 0.05 significance level (actual value is 0.0461).

I. Multiple Comparisons

No control for the effect of multiple comparisons is planned.

J. Analysis Populations

Five analysis populations will be defined for use with various analyses. The following table illustrates the relationship between each population and the analyses for which the data from the population will be used.

Analysis Population	Analysis					
	Baseline	Patient Disposition	Efficacy	Safety	Pharmaco-dynamic	PK
Modified Intent-to-treat (mITT) Population			X			
Response Evaluable Population			X			
Safety Population	X	X		X		
Pharmacodynamic Population					X	
Pharmacokinetic (PK) Population						X

1. mITT Population

The mITT population consists of patients enrolled in Phase 2a and the Phase 2b who meet the eligibility criteria and received at least 1 dose of study drug (*i.e.* BXCL701 or PEMBRO depending on cohort).

2. Response Evaluable Population

In Phase 2a for U.S. site, the response evaluable population consists 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 2a for UK site, the response evaluable population consists 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).

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.

3. **Safety Population**

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

4. **Pharmacodynamic Population**

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

5. **PK Population**

   The PK population includes 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.

K. Subgroups Analysis

Subgroup analysis is not planned.

L. Data Display Characteristics

Data displays produced for this study will include three types—summary tables, data listings, and figures. Unless stated otherwise, data listings will be produced for all recorded data. Summary tables will be produced as specified in following sections. Additional data listings will be produced for outcome measures that involve extensive procedures to derive the analyzed outcomes.

Data listings will list the data recorded on the CRF or derived for each patient. They will be ordered by study stage, dose group, patient ID, and time of assessment. When expedient, additional levels of ordering hierarchy may reflect subsets of assessments within patient. Data listings will not display patient initials.

Summary tables will display summary statistics calculated for each of the dose groups and all patients combined in each study stage, unless described otherwise in following sections. For most summary tables, the dose groups will be presented in columns and the summary statistics of interest will be presented in rows. Additional column will summarize the total experience for patients within the mCRPC histologic subtype from the Phase 2a and Phase 2b.

Summary statistics displayed will be a function of the type of data associated with the summarized assessment. Unless stated otherwise in relevant sections to follow, continuous data will be summarized with the number of non-missing values, mean, standard deviation, minimum, median, and maximum. Categorical data will be summarized with the number of non-missing values and the numbers of values equal to each of the possible values. Percentages of patients with each of the possible values will be calculated from the number of patients in the corresponding analysis population, unless stated otherwise. Some continuous variables may also be grouped into categorical levels and evaluated in frequency tables.

M. Blinded Review of Data

This is an open-label study. No blinded review is planned.

VII. Patient Accountability

A. Patient Characteristics

Demography and Baseline Characteristics. Data collected about the following patient characteristics at the screening visit will be presented in summary tables and data listings for the safety 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.

- Age. Age will be calculated as the number of years elapsed between birth date and the date of the screening visit, adjusted for whether the birthday has passed as of the day of the screening visit (this corresponds to the typical calculation of age a person would use in conversation).
- Race. American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other, Not Reported
- Ethnicity. Hispanic or Latino, Not Hispanic or Latino, Not Reported
- Height (cm)
- Weight (kg)
- Body mass index (BMI)
- Eastern Cooperative Oncology Group (ECOG) Performance Status

Medical History. Medical history will be coded using MedDRA dictionary, version 21.1 or higher and summarized for the safety population by system organ class (SOC) and preferred term (PT).

Cancer History. Disease history will be tabulated for all safety patients in the Phase 1b, Phase 2a, Phase 2b and overall respectively. The summary will include time since initial diagnosis, tumor nodes metastasis (TNM) Staging (T, N and M

categories) at initial diagnosis, initial diagnosis, most recent diagnosis, time since diagnosis of confirmed metastatic disease, PSA results within one year prior to inform consent date, and baseline disease sites.

Prior Systemic Anti-Cancer Therapy. A summary of number of previous regimens, number of previous therapies for prostate cancer, reason for regimen, and best overall response to prior anti-cancer therapy (complete response [CR], partial response [PR], stable disease [SD], disease progression, or Unknown) will be provided. Number of subjects with chemotherapy alone, radiotherapy alone, chemotherapy + radiotherapy will be tabulated. The following chemotherapy categories will be summarized as well: androgen signaling inhibitors (ASI), 1st generation ASI, 2nd generation ASI, taxane chemotherapy, Provenge® (Sipuleucel-T).

Prior Anti-Cancer Systemic Therapy will be coded using WHO Drug September 2018, and summarized for the safety population by anatomical main class (1st level) and pharmacological subgroup (3rd level).

Prior Radiotherapy. Prior Radiotherapy will be tabulated for the safety population. The summary will also include the number of patients with prior radiotherapy for cancer, the number of patients with prior radiotherapy for prostate cancer, the number of previous radiotherapies, the number of previous radiotherapies for prostate cancer, reason for regimen, radiotherapy location.

Prior Anti-Cancer Surgery. Prior Anti-Cancer Surgery will be coded using MedDRA dictionary, version 21.1 or higher, and summarized for the safety population by system organ class (SOC) and preferred term (PT). The summary will also include the number of patients with prior surgery for cancer, the number of patients with prior surgery for prostate cancer, the number of previous surgeries, the number of previous surgeries for prostate cancer, surgery intent, surgery location and time between last surgery to study enrollment.

B. Disposition

A summary table of patient disposition as recorded during the study exit and end of treatment visit will summarize the numbers of patients in the safety population with columns for Phase 1b, Phase 2a, Phase 2b, and overall by disease subtype. Counts and percentages of patients who withdrew for each of the reasons on the End of Treatment form will be calculated using the number of patients in the relevant cohort as the denominator. Reasons for discontinuing BXCL701 or PEMBRO will be summarized separately. The reasons for BXCL701 or PEMBRO discontinuation include:

- *Adverse Event*
    - *Related to Study Drug*
    - *Unrelated to Study Drug*
- *Investigator Decision*
- *Patient Non-Compliance/Protocol Violation(s)*

- *Protocol Defined Disease Progression*
- *Study Terminated by Investigator or Sponsor*
- *Withdrawal of Consent*

In addition, the termination reasons for end of study as recorded on that visit, will be calculated and presented by reason:

- *Death*
- *Lost to Follow-Up*
- *Study Terminated by Sponsor*
- *Withdrawal of Consent*

A listing of treatment discontinuation and study discontinuation data will also be generated for patients in the safety population.

C. Protocol Deviations and Population Inclusions

A listing of patients displaying eligibility for each analysis population will also be generated and will include the dates of informed consent.

All enrolled patients will be displayed in another listing that includes the protocol version under which they enrolled, and whether all inclusion/exclusion criteria were satisfied.

Listing of protocol deviations will be provided separately for major and minor deviations. The clinical team will review periodically the protocol deviations and will finalize the deviations prior to the database lock.

VIII. Efficacy Analyses

A. Definition of Efficacy Outcomes

In Phase 2a, the primary efficacy outcome is the Composite Response Rate.

Composite Response Rate is defined as the proportion of patients achieving 1 or more 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.

Only patients with CTC ≥5/7.5mL at baseline should be included in the CTC conversion assessment.

In Phase 2b, the primary objective is response rate by RECIST 1.1 criteria.

The secondary efficacy outcomes are defined below.

Objective response rate is defined as the number (%) of patients with a CR or PR among patients with evaluable lesions by RECIST1.1. Response will be

determined by RECIST 1.1 Criteria. Objective response rate is a secondary objective in Phase 2a only.

Composite Response Rate is a secondary objective in Phase 2b only. It 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.

Radiographic PFS (rPFS) is defined as the time from the date of initiation of protocol therapy to date measurement criteria are first met for PD by RECIST 1.1/ PCWG3 criteria or death from any cause, whichever occurs first. Objective response rate is a secondary objective in both Phase 2a and Phase 2b.

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 if subsequent anti-cancer therapy occurs before PD. One day will be added to each calculation to account for the designation of the first day of treatment as Study Day 1.

Prostate-Specific Antigen Progression-Free Survival (PSA PFS) is defined as the time from the date of initiation of protocol therapy to 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. Objective response rate is a secondary objective in both Phase 2a and Phase 2b.

Overall Survival (OS) is the difference between the date of death and the first date of study treatment (+1 day). Patients who do not expire 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. Objective response rate is a secondary objective in both Phase 2a and Phase 2b.

Duration of Response is defined as the time interval 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. Objective response rate is a secondary objective in both Phase 2a and Phase 2b.

Immunology Progression-Free Survival (iPFS) is defined as the time from the date of initiation of protocol therapy to date measure criteria are first met for PD

by iRECIST criteria or death from any cause. Subjects who meet the criteria for PD by RECIST 1.1/PCWG3 but not iRECIST and who discontinue treatment will be censored at the date of PD.

PSA_{50} Duration of Response (PSA DOR) is defined as the time interval between the first date when PSA declined 50% or more from baseline and the date on which PSA progression is confirmed or death from any cause, whichever occurs first. Patients who do not experience PSA progression 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 PSA assessments verified lack of PSA progression.

Duration of Stable Disease by RECIST 1.1 is defined as the time interval between the first date when the criteria for Stable Disease (SD) 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.

B. Primary Efficacy Outcome Analysis

The primary efficacy analysis will use data from the Response Evaluable Population.

In Phase 2a, the composite response rate is calculated as the number (%) of patients achieving 1 or more specified response criteria among the response evaluable population. In phase 2b, the objective response rate is calculated as the number (%) of patients achieving confirmed CR or PR by RECIST 1.1 criteria. Two-sided 95% confidence interval (CI) will be calculated using Exact Binomial method. Patients with missing composite endpoint will be considered non-responders (e.g., not 1 of the 3 criteria for composite endpoint is met in Phase 2a). In addition, in Phase 2b, the two-sided 80% confidence interval for the difference in response rates [6] will be calculated to inform proof-of-concept.

In Phase 2a, the composite endpoint rate across 2 stages and its two-sided exact 95% CI will be calculated as if data were collected in a single stage. This approach that ignores the sequential statistical testing may lead to biased point estimate of the composite endpoint rate and the CI may not provide the stated coverage probability but is generally accepted when the event rate is relatively small.

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.

C. Secondary Efficacy Outcomes Analyses

1. Objective Response Rate (Phase 2a only)

The objective response rate (ORR) will be estimated among the patients in the Response Evaluable Population who have evaluable lesions by RECIST 1.1. Patients in the Response Evaluable Population with evaluable lesions by RECIST1.1 with missing objective response will be considered as non-responders. Confirmation of CR or PR as PR/CR on two consecutive imaging assessments separated by at least 28 days is required per RECIST 1.1 (Please check the Appendix No.1 for detailed rules).

The response categories by RECIST 1.1 include: CR, PR, SD, PD, and unable to assess (UTA). The best overall response will be selected based on the order of CR, PR, SD, PD, and UTA.

ORR and its exact 95% CI will be calculated as if data were collected in a single stage without considering the two-stage design.

In addition, best overall response will also be tabulated in the categories of CR, PR, unconfirmed CR, unconfirmed PR, SD, PD, and UTA.

Target lesions, non-target lesion, new lesion, and response data will be listed.

2. Composite Response Rate (Phase 2b only)

As part of the composite response, objective response will be calculated using the same method stated in section VIII.C.1.

In the second criterion of the composite response, PSA decline from baseline will calculated among patients in the Response Evaluable Population who has PSA measured as baseline and at least once post-baseline. Patients are considered as PSA responders if they have 50% or greater PSA decline from baseline.

3. Time-to-event outcomes

The primary time-to-event analysis will be performed using the Response Evaluable Population.

The distribution of time-to-event response including rPFS, iPFS, PSA PFS, DOR, PSA DOR, duration of SD and OS will be estimated by Kaplan-Meier methodology. The medians of these time-to-event efficacy parameters, if available, and their two-sided 95% CIs, will be reported. In addition, milestone rates at selected time points (e.g. 3 months, 6 months, 9 months, 12 months, etc.), together with their 2-sided 95% CI will be presented. The calculations will be performed based on fixed sample, single stage design.

Analyses on duration of overall objective response will be performed for the Response Evaluable Population who achieve confirmed PR or CR. The

number of CR and PR patients may be small, and thereby limit use of the Kaplan-Meier method to provide reliable information. In this case, descriptive statistics or listings will be provided.

After discontinuing the study medication, patients may be treated with additional therapy. Data collected after patients have been treated with additional therapy will not be used to evaluate the duration of objective response.

4. **Analysis of Cytokine Levels**

The analysis of the secondary efficacy endpoints including cytokine levels will be reported for the pharmacodynamic analysis population. There will be a separate SAP for analyses of cytokine levels.

D. Analysis of Exploratory Efficacy Endpoints

The exploratory endpoints will be analyzed using the Response Evaluable Population.

Response rate by iRECIST criteria and its two-sided exact 95% CI will be calculated as if data were collected in a single stage without considering the two-stage design.

The response categories by iRECIST include: complete response (iCR), partial response (iPR), stable disease (iSD), Unconfirmed Progressive Disease (iUPD), Confirmed Progressive Disease (iCPD), and unable to assess (UTA). The best overall response will be selected based on the order of iCR, iPR, iSD, iUPD, iCPD, and UTA. Response rate by iRECIST criteria will be reported for every phenotype in Phase 2a, Phase 2b, and combined.

Whenever feasible, cross tabulation of clinical outcomes by presence/absence of relevant immune effector cytokines and various immunological effector cells in blood and tumor tissues will be presented.

The baseline PD-L1 tumor expression in metastatic tumor tissue and CTCs will be cross-tabulated with subsequent clinical outcomes. Baseline tumor mRNA immune profiling panel will be cross-tabulated with clinical outcomes with regards to response and safety. Summary of bone scan will be tabulated.

IX. Safety Analyses

Safety analyses will use data from the Safety Population. Relevant safety data from visits with scheduled assessments will be presented in summary tables and data listings as described below for data collected on the study drug administration, adverse event (AE), vital signs, concomitant medication, electrocardiogram (ECG), ECOG, and clinical laboratory (e.g. chemistry, hematology, and urinalysis) eCRF pages.

A. Exposure

Exposure to BXCL701 and PEMBRO will be summarized using the dosing data entered into the BXCL701 Drug Administration, PEMBRO Drug Administration

and BXCL701 Accountability eCRF, and will be summarized in tables. Data will be summarized by dose group and study Stage and overall, for the following exposure measures, separately for BXCL701 and PEMBRO:

- *Number of Cycles Initiated* (for BXCL701 only)
- *Total Number of Dose Administered* (for PEMBRO only)
- *Cumulative Dose Received* (mg). Defined as total dose received from first dose date up to and including last dose date
- *Dose Intensity*. Defined as [total cumulative dose (mg) / (duration of dosing in cycles)]
- *Relative Dose Intensity*. Defined as the percentage of planned dose. Calculated as [actual cumulative dose (mg) / (planned cumulative dose (mg)], expressed as a percent
- *Number of Subjects with Dose Increase From .4mg TDD to .6mg TDD* (for BXCL701 only)

The number and percent of patients with BXCL701 dose reduced, dose missed, dose held, and drug permanently discontinued will be summarized. The reasons for each dose modification or discontinuation will also be summarized.

Similarly, the number, percentage, and reasons of PEMBRO infusion held, infusion interrupted, and drug permanently discontinued will be summarized. The reasons for each dose modification or discontinuation will also be summarized.

Study drug exposure to BXCL701 and PEMBRO and dose modifications or interruption will also be presented in data listings.

B. Adverse Events

The following details will be collected for each AE: description of the AE, start date and stop date, CTCAE grade, relationship to BXCL701, action taken with BXCL701, relationship to PEMBRO, action taken with PEMBRO, relationship to study specific procedure, other action taken, outcome, whether AE was a dose-limiting toxicity (DLT), and whether the AE was serious or not. The data will be tabulated by study stage and dose schedule, and number (%) will be displayed. The data will be listed as well.

Per the protocol, 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.

AEs will be coded using MedDRA, v21.1 or higher, and graded using NCI CTCAE v5.0, associating lower-level terms with preferred terms and system

organ classes by the primary hierarchy. Preferred terms may be grouped upon medical review. A Treatment-Emergent Adverse Event (TEAE) is an AE occurring on / after the date of first BXCL701 / PEMBRO dose and within 30 days of the last dose of BXCL701 / PEMBRO. TEAEs will display counts and percentages of patients who reported at least one AE in each system organ class. Within each system organ class, the tables will display the counts and percentages of patients reporting at least one preferred term.

Summary tables of TEAEs by default MedDRA System Organ Class (SOC) and Preferred Term (PT) will be sorted by decreasing order of frequency of SOC, and then, within that, by decreasing order of frequency of PT in the All Patients with Adenocarcinoma group. An AE reported by a patient more than once will be represented in the most severe category reported.

The following AE summary tables displaying counts and percentages of patients with AEs will be produced:

- Overall summary of TEAEs
- All TEAEs by System Organ Class and Preferred Term
- TEAEs related to BXCL701 and separately for PEMBRO by system organ class and preferred term. TEAEs related to BXCL701 or PEMBRO by system organ class and preferred terms. These tables will include TEAEs with a drug relationship of “Related” or “Possibly Related.” An AE reported by a patient more than once will be included in this table if at least one of the drug association relationships is one of the relationships listed here
- Serious TEAEs by system organ class and preferred term
- Serious TEAEs related to BXCL701 and separately for PEMBRO by system organ class and preferred term. These tables will include TEAEs with a drug relationship of “Related” or “Possibly Related”
- Serious TEAEs related to BXCL701 or PEMBRO by system organ class and preferred term
- TEAEs leading to any study drug discontinuation, BXCL701 discontinuation, and PEMBRO discontinuation, respectively, by system organ class and preferred term. This subset includes TEAEs with an Action Taken of “Drug Permanently Discontinued”
- TEAEs leading to BXCL701 dose reduced by system organ class and preferred term
- TEAEs leading to BXCL701 dose held by system organ class and preferred term
- TEAEs leading to PEMBRO dose held by system organ class and preferred term

- TEAEs leading to PEMBRO dose interruption by system organ class and preferred term
- TEAEs with CTCAE Grade ≥3 by system organ class and preferred term
- TEAEs related to BXCL701 and separately for PEMBRO with CTCAE Grade ≥3 by system organ class and preferred term
- TEAEs related to BXCL701 or PEMBRO with CTCAE Grade ≥3 by system organ class and preferred term
- TEAEs leading to death by system organ class and preferred term
- TEAEs by System Organ Class and Preferred Term, and CTCAE Grade. On this table, treatment groups will be subdivided into five potential grades of AE severity, based on the NCI CTCAE, version 5.0. An AE reported by a patient more than once will be represented in the most severe category
- TEAEs related to BXCL701 by System Organ Class and Preferred Term, and CTCAE Grade
- TEAEs related to PEMBRO by System Organ Class and Preferred Term, and CTCAE Grade
- TEAEs related to BXCL701 or PEMBRO by System Organ Class and Preferred Term, and CTCAE Grade
- Serious TEAEs by System Organ Class and Preferred Term, and CTCAE Grade
- Serious TEAEs related to BXCL701 by System Organ Class and Preferred Term, and CTCAE Grade
- Serious TEAEs related to PEMBRO by System Organ Class and Preferred Term, and CTCAE Grade
- Serious TEAEs related to BXCL701or PEMBRO by System Organ Class and Preferred Term, and CTCAE Grade
- TEAEs by Preferred Term
- TEAEs related to BXCL701 by Preferred Term
- TEAEs related to PEMBRO by Preferred Term
- TEAEs related to BXCL701 or PEMBRO by Preferred Term

The AE listings shown here will be produced, sorted chronologically within patient. Each listing will include system organ class, preferred term, CTCAE grade, outcome, event start and stop dates, relation to each study drug, action taken with each study drug, other action taken, and SAE status. DLT status will only be reported for patients in the Phase 1b.

- TEAEs

- AEs. The listing includes all AEs reported in EDC
- TEAEs related to BXCL701 and separately for PEMBRO
- TEAEs related to BXCL701 or PEMBRO
- Serious TEAEs
- Serious TEAEs related to BXCL701 and separately for PEMBRO
- Serious TEAEs related to BXCL701 or PEMBRO
- TEAEs leading to any study drug discontinuation, BXCL701 discontinuation, and PEMBRO discontinuation, respectively
- TEAEs leading to BXCL701 dose reduced
- TEAEs leading to BXCL701 dose held
- TEAEs leading to PEMBRO dose held
- TEAEs leading to PEMBRO dose interruption
- TEAEs with CTCAE Grade ≥ 3
- TEAEs leading to death

C. Death

A summary table and listing of patients who died while on study will be generated and will display the cause of death and time to death from the date of initiation of protocol therapy.

D. Clinical Laboratory Results

For each hematology, chemistry, and urinalysis laboratory parameter, the following analyses will be performed:

- Summary tables displaying the number of non-missing values, mean, standard deviation, median, and range (minimum and maximum) for baseline, minimum and maximum values post-baseline, worst change post-baseline, last observation post-baseline, and change of last observation post-baseline. Change from baseline will be calculated as the post-baseline measurement minus the baseline measurement. If either the baseline or post-baseline value is missing, the observation will not be included in the change from baseline summary.
- Shift tables summarizing the counts and percentages of patients by CTCAE severity grade at baseline and at the worst post-baseline result, for those per-protocol lab parameters that are graded according to the Common Toxicity Criteria (NCI CTCAE v5.0).
- Shift tables summarizing the counts and percentages of patients by reference range indicator (Low, Normal, High), for those per-protocol lab parameters that no CTCAE grading exists.

All laboratory test results (including hematology, chemistry, and urinalysis) will also be presented in data listings for the Safety Population. Any out-of-range values will be flagged in the data listings and a list of clinically significantly abnormal values will be presented.

E. Vital Signs

Vital signs (including weight, temperature, pulse rate, respiratory rate, sitting systolic and diastolic blood pressure, standing systolic and diastolic blood pressure) will be summarized and presented in summary tables as actual and change from baseline for each dose cohort in each study stage at each scheduled assessment. The number of non-missing values, mean, standard deviation, median, and range (minimum and maximum) will be presented. Change from baseline will be calculated as the post-baseline measurement minus the baseline measurement. If either the baseline or post-baseline value is missing, the observation will not be included in the change from baseline summary.

A listing of all vital sign assessments will be presented for the Safety Population.

F. Concomitant Medications

Concomitant medication is defined as any medication with a start date prior to the date of the first dose of study treatment and continuing after the first dose of study treatment or with a start date between the dates of the first and last dose of study treatment, inclusive. Any medication with a start date after the date of the last dose of study treatment will not be considered a concomitant medication. Any medication with a stop date prior to the first dose of study treatment is defined as a prior medication.

Concomitant medications will be coded using WHODrug September 2018 or higher version. Summary tables will be organized to display the anatomical main class (1st level) of each coded medication and, within that, the pharmacological subgroup (3rd level) of the coded medication. The summary tables will display counts and percentages of patients who reported using at least one medication in each represented pharmacological subgroup.

A listing of concomitant medications will be generated for the Safety Population and will display entries from the Concomitant Medications eCRF page, ordered within patient by the "Date Started." The listing will display the recorded term from the CRF and, adjacent to that, the WHODrug pharmacological subgroup and the anatomical main class that appears in the tables.

version.

G. Electrocardiogram (ECG)

Shift to post-baseline table by each visit and shift to worst post-baseline will be presented for ECG interpretation data. A listing of ECG data including QTcB at the baseline will be provided.

H. ECOG Performance Status

A listing of ECOG Performance Status results for assessments made during the study will be generated.

X. Pharmacokinetic Analysis

PK concentration data will be generated by Northeast Bioanalytical Laboratories LLC. The analyses for the PK data will be described in a separate analysis plan.

XI. References

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XII. Appendix

1. Best Overall Response by RECIST Guideline

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.
a If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.