STATISTICAL ANALYSIS PLAN

A Phase 1b/2a Trial Adding X4P-001 in Patients Receiving Nivolumab for Treatment of Advanced Clear Renal Cell Carcinoma

Protocol Number:	X4P-001-RCCB
Protocol Version and Date:	V3.0 July 05, 2017
Study Drug Name:	X4P-001
Phase:	Phase 1b/2a
Sponsor:	X4 Pharmaceuticals, Inc.
Analysis Plan Date:	September 14, 2018
Analysis Plan Version:	Version 1.1

SPONSOR SIGNATURE PAGE

Protocol Title:	A Phase 1b/2a Trial Adding X4P-001 in Patients Receiving Nivolumab for Treatment of Advanced Clear Cell Renal Cell Carcinoma
Protocol Number:	X4P-001-RCCB
Sponsor:	X4 Pharmaceuticals, Inc. 955 Massachusetts Ave, 4th Floor Cambridge, MA 02139

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidance and guidelines.

Author

[redacted] Signature:

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LLX Solutions, LLC

Approver:

[redacted] Signature:

[redacted] Date:

X4 Pharmaceuticals, Inc.

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ABBREVIATIONS

Abbreviation	Explanation
aCSR	Abbreviated Clinical Study Report
AE	Adverse Event
ccRCC	Clear Cell Renal Cell Carcinoma
CE	Clinically Evaluable
CR	Complete Response
CRF	Case Report Form
CS	Clinically significant
CXCL12	C-X-C Chemokine Ligand Type 12 (also designated SDF-1)
DCR	Disease Control Rate
ECG	Electrocardiogram
iRECIST	Response Evaluation Criteria in Solid Tumors for immune-based therapeutics
ITT	Intent-to-Treat
MDSCs	Myeloid-derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Non-Clinically significant
ORR	Objective Response Rate
PBMC	Peripheral blood mononuclear cell
PD	Progressive Disease
PFS	Progression Free Survival
PK	Pharmacokinetics
PR	Partial Response
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SOC	System Organ Class
STD	Standard Deviation
TEAE	Treatment Emergent Adverse Event
TLT	Treatment-Limiting Toxicity
Treg	T Regulatory
TTP	Time to Progression
WBC	White Blood Cell
WHO	World Health Organization

1 INTRODUCTION

This statistical analysis plan is designed to outline the statistical methods in evaluating the safety and tolerability of X4P-001 used in combination with nivolumab in patients tolerating nivolumab but not exhibiting radiologic response in study protocol X4P-001-RCCB.

This document has been prepared protocol version 3.0 dated 5th July 2017 and Case Report Form (CRF) dated 12th October 2017. X4 Pharmaceuticals is terminating this study early due to the poor enrollment rate. An abbreviated clinical study report (aCSR) will be written for this study. This report will describe all the safety and the selected efficacy information.

Biomarker specific analyses will be provided in a separate statistical analysis plan.

2 STUDY DESIGN OVERVIEW

2.1 Overall Study Design

This is a single-arm, open-label and multicenter study to characterize the safety and tolerability of adding X4P-001 to nivolumab treatment in patients with advanced ccRCC. Eligible patients who have received nivolumab and have demonstrated a confirmed best response of SD or radiologic progression (PD) without clinical deterioration, as assessed by their Investigator, will be enrolled into study.

Up to 20 patients may receive the protocol-specified combination treatment and continue until either:

- Treatment-Limiting Toxicity (TLT), as defined for X4P-001 and as per approved label for nivolumab.
- PD, based on either clinical or radiologic assessments, using findings at study entry to define the baseline.
- Patients that meet radiologic criteria for progression compared with study baseline as defined by RECIST v1.1 may continue in the study if their Investigator judges that both of the following apply: (a) the patient is likely to benefit from ongoing treatment with study treatment; and (b) the patient does not have clinically significant symptoms of PD.
- Any patient with subsequent imaging demonstrating immune confirmed progressive disease (iCPD) based on iRECIST criteria must discontinue study treatment.

To protect patients' safety, a Data Review Committee will review available safety data and make a recommendation on the progress of the study during study treatment.

The study schedule is presented in Table 1.

Table 1: Schedule of Events

Event[1]	Screen[2]	Cycle 1				Even-numbered cycles ≥#2		Odd-numbered cycles ≥#3		EOT[3]	EOS[4]
Day # within Cycle[5]		1	8	15	22	1	15	1	15		
Informed Consent	X										
Medical History, including RCC	X										
ECOG Performance Status	X	X				X		X		X	X
PE, body weight, body height[6,7]	X[7]	X				X		X		X	X
Vital signs[8]	X	X	X	X	X	X	X	X	X	X	X
CT imaging[9]	X							X		X	
Hematology & Chemistry[10]	X[11]	X	X	X	X	X		X		X	X
TFTs, Coagulation & U/A[12]	X[11]	X[12]						X[12]		X[12]	
12-lead ECG	X	X			X[23]			X		X	X
Ophthalmologic Examination[13]	X[14]							X		X	
Pregnancy test[15]	X	X						X		X	X
Pre-dose PK Sample		X	X	X				X[16]			
Dense PK & PD Sampling[17]					X						
Blood biomarker collection[18]		X			X			X		X	X
Archived tissue[19]	X										
Administration of nivolumab[20]		X[21]		X		X	X	X	X		
X4P-001 dosed in clinic[22]		X[23]	X	X	X			X[16]			
AE & Con Med Monitoring	From screening to End of Study Visit										

1. The schedule is presented relative to Cycle and Day within Cycle. The calendar day of the first administration of study drug is designated Day 1. Each Cycle represents 4 weeks (28 days). Pre- and post-dose intervals are relative to the time of oral administration of study drug, designated 0 hr.
2. Screening may be initiated up to 28 days prior to Day 1. Confirmation of eligibility will be done by Sponsor review prior to enrollment
3. The EOT visit will be performed ≤6 days after the last dose of study drug or the decision to terminate treatment.
4. The EOS visit is scheduled for 30 days (±4 calendar days) after the last dose of study drug. In the event the EOT visit is delayed, the EOS visit will be performed at least 14 days after the EOT visit.
5. To allow for scheduling flexibility, on-treatment visits may be done within ±3 calendar days of the day indicated.
6. At Screening, EOT, and EOS, complete physical exam (PE); at other visits, exams focused on areas of disease or AEs.
7. Body height is collected at screening only.
8. Vital signs comprise heart rate, blood pressure, and temperature. For patients dosed in clinic for PK collections, vital signs will be performed pre-dose.
9. CT (chest, abdomen, and pelvis) – for screening purposes, imaging performed as standard of care may be used if done ≤28 days prior to Day 1; while on-treatment, imaging may be performed with a window of ±4 calendar days; at EOT, imaging is not required if performed in the prior 4 weeks.
10. Hematology and chemistry laboratory tests may be obtained up to 3 days prior to visit; performed at local lab; For patients dosed in clinic for PK collections, safety laboratory tests will be collected pre-dose.
11. Safety laboratory testing for eligibility should be performed within 14 days prior to Cycle 1 Day 1; performed at local lab.
12. TFTs, Thyroid Function Tests; Coagulation studies and U/A (urinalysis) performed at Screening and EOT only; performed at local laboratory.
13. Ophthalmologic examination may be performed with a window of ±4 calendar days.
14. Screening ophthalmologic exam reports and retinal photos must be submitted to the sponsor at least 5 business days prior to Cycle 1 Day 1 to allow central review for eligibility. See study pperational manual for additional details.
15. Pregnancy tests, applicable only to women of childbearing potential, may be urine or serum test. On Day 1, the test results will be obtained prior to dosing. Performed at local lab.
16. Pre-dose PK sample and X4P-001 dosing in clinic only at Cycle 3.
17. See protocol Sections 7.1.2 and 7.1.3.1 for details of sample collection times for dense PK (central lab) and PD (local lab).
18. Blood samples for biomarkers; processed at site and shipped to central laboratory.
19. Site to confirm availability of archived tumor tissue.
20. Administration of nivolumab.

21. Patients should be observed for at least 1 hour after their 1st dose of X4P-001 before receiving nivolumab, then observed for at least 1 hour after nivolumab infusion on Cycle 1 Day 1.
22. X4P-001 will be self-administered by the patient, except at PK visits, when it will be administered in the clinic.
23. On Day 1, dispense eye drops and nasal spray.
24. ECG assessment performed at 2 hr post-dose (± 15 min).

2.2 Sample Size

Up to 20 patients are planned to be enrolled. With a sample size of 20 patients, there is an estimated 95% probability of observing at least once any AE (including TLT) that has an incidence rate of 14% or higher.

Although the sample size is based on feasibility rather than statistical power, the results of the study will be used to provide a preliminary estimate of the effect size. The sample size of 20 patients will be sufficient to exclude a low threshold rate of response to treatment. Specifically, if an ORR of 20% or higher is observed, then the lower bound of the 95% exact confidence interval for the proportion of responders exceeds the threshold rate of 5%. This would support further studies of the combination of nivolumab and X4P-001.

2.3 Randomization and Blinding

This is an open-label Phase 1b/2a study. Patients will not be randomized to study treatment.

3 STUDY OBJECTIVES

3.1 Primary Objectives

- To characterize the safety and tolerability of X4P-001 used in combination with nivolumab in patients tolerating nivolumab but not exhibiting radiologic response.

3.2 Secondary Objectives

- To characterize the pharmacokinetics (PK) of X4P-001 when used in combination with nivolumab.
- To characterize the antitumor activity of the combination of X4P-001 and nivolumab.

3.3 Exploratory Objectives

- To investigate selected peripheral blood biomarkers of immune activation during treatment with X4P-001 plus nivolumab.
- To evaluate archived tumor tissue for biomarkers that may correlate with response to combination treatment with X4P-001 and nivolumab.
- To assess the treatment effect (clinical activity) of the combination of X4P-001 and nivolumab in patients with advanced ccRCC using modified Response Evaluation Criteria in Solid Tumors for immune-based therapeutics (iRECIST)

4 STUDY ENDPOINTS AND EVALUATIONS

4.1 Safety Evaluations

- Treatment emergent adverse events (TEAEs)
- Clinical laboratory assessments
  - Hematology
  - Serum chemistry
  - Coagulation factors
  - Pregnancy tests
  - Urinalysis
  - Thyroid function
- Physical examination findings (including weight)
- Ophthalmologic examination
- Vital signs
- ECOG performance status
- ECG findings

4.2 Efficacy Endpoints and Evaluations

- ORR, defined as proportion of patients with best overall response of CR or PR
- Time to objective response, defined as time from first administration of combination regimen to first CR or PR whichever comes first.
- Duration of response (DOR), defined as the time from first CR or PR whichever comes first until the time of disease progression by RECIST v1.1 or death by any cause.
- Disease control rate (DCR), defined as proportion of patients with best overall response of CR, PR or SD
- PFS, defined as the time from first administration of combination regimen until objective tumor response or death from any cause
- Time to progression (TTP), defined as the time from first administration of combination regimen until objective tumor progression

4.3 Biomarker Evaluations

- Identification of potential biomarkers that may predict response to combination treatment with X4P-001 and nivolumab

Biomarker analysis will be provided in a separated analysis plan.

4.4 Pharmacokinetics Evaluations

- Plasma or serum concentrations
- Pharmacokinetics parameters
  - Area under the concentration-versus-time-curve (AUC)
  - Maximum concentration (C_{max})
  - Time to reach maximum concentration (T_{max})

4.5 Pharmacodynamic Evaluations

- Effect of study treatment in WBCs including absolute neutrophil counts and absolute lymphocyte counts in blood

4.6 Other Evaluations

- Baseline and demographic characteristics
- Serology test at baseline
- Medical history
- Prior cancer treatment/ procedures for renal cell carcinoma
- Previous and concomitant medications
- Prognosis factors

5 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

5.1 Definition of Baseline

For all evaluations unless otherwise noted, baseline is defined as the most recent non-missing measurement prior to the first administration of study drug.

5.2 Study Event Days and Times

Study events will be recorded using the calendar date and (where applicable) the time to the nearest minute. For purposes of post-study analysis (e.g., tables and listings), study days will be designated as follows:

- Day 1 is defined as the calendar day of the first dose of study drug.
- The days prior to Day 1 are designated Day -1, Day -2, etc.; there is no Day 0.
- The days following the day of the first dose of study drug are designated Day 2, Day 3, etc.
- The day of the dose of study drug is indicated by adding the suffix "L", e.g., if the last dose is administered on Day 43, it will be displayed as "Day 43L". The days following the last administration of study drug are designated Day 1P, Day 2P, etc.

The times of events related to dosing of study drug will be designated as minutes or hours before or after the time of dosing, which is designated as t=0 (zero). Thus, 15 minutes prior to dosing is t = -15 min; 2 hours after dosing is designated t =2 h.

5.3 First Dose Date of Study Treatment

The date of first dose of study treatment is defined as the earliest dose date of study drugs in the treatment regimen.

5.4 Analysis Visit Window

For safety parameters as described in Section 4.1 excluding clinical laboratory data, measurements collected from unscheduled visits will not be included in the by-visit summary tables but will be included in the listings. Early termination visits for safety measurements will not be mapped to any scheduled post-baseline visit but will be used as the last assessment during treatment period.

5.5 Safety Data Handling

For all safety data, only observed data will be used for analyses, and missing data will not be imputed.

Missing values for safety measures at baseline such as laboratory data, vital signs and ECG data will be substituted by values from the screening visit, where available.

5.5.1 Handling of Repeated Clinical Laboratory Tests

For laboratories results at unscheduled visits, it will be treated as repeated laboratory results for the closest previous visit. The worst results within the visit will be used in the summary tables for that visit.

Lab results beyond the detectable limits will be reported as detectable limits for calculating descriptive statistics.

All the laboratory test results will be included in the data listings as reported.

5.5.2 Handling of Partial Dates

Partial or missing dates will be handled as follows:

- For adverse events, imputation of missing or partial dates will only be performed to determine treatment emergence. Unless the partial portion of the date or the corresponding end date indicates otherwise, partial and missing start dates will be assumed to be the date of first dose of study medication to conservatively report the event as treatment emergent. If the partial date or the corresponding end date indicates otherwise, the rules for all other data types should be followed as described below.
- For medications, imputation of partial dates will only be performed to determine whether a medication is concomitant. Unless the partial portion of the date indicates otherwise, partial start and end dates will be assumed to be the date of first dose of study medication to conservatively report the medication as concomitant. If the partial dates indicate otherwise, the rules for all other data types should be followed as described below.
- For all other data types (e.g. date of initial diagnosis), if there are partial dates which require imputation for calculations, the day and/or month and/or year will be imputed in a conservative manner; i.e. for the start dates, if only the day is missing, it will be imputed with the first day of the month and if the month is also missing, it will be imputed with the 1st January. For the end dates, if only the day is missing, it will be imputed with the last day of the month and if the month is also missing, it will be imputed with the 31st December.

6 PLANNED ANALYSIS

6.1 Changes from Planned Analyses in the Protocol

As X4 Pharmaceuticals has decided to terminate this study early, and to summarize the study with an aCSR, not all data collected in this study will be analyzed. Summary statistics will only be presented for patient disposition, baseline characteristics, exposure of study drug, AEs, laboratory values (hematology, clinical chemistry, coagulation and thyroid function), vital signs, ECG, ophthalmological examination, ORR, DCR and biomarkers.

6.2 Interim Analysis

There is no formal provision for an interim analysis in this early phase study.

6.3 Final Analyses and Reporting

All final planned analyses per protocol and this analysis plan will be performed only after database lock.

7 ANALYSIS POPULATIONS AND APPLICATIONS

7.1 All Patients Population

All Patients Population includes all patients who sign an informed consent form (ICF).

7.2 Safety Population

The Safety Population is defined as all patients who receive at least one dose of study medication.

7.3 Intent-to-Treat Population

The Intent-to-Treat (ITT) population is defined as all patients who receive at least one dose of study medication. This population will be used for efficacy summaries.

This population is identical to the Safety Population.

7.4 Clinically Evaluable Population

The Clinically Evaluable (CE) Population is defined as all patients who have adequate data at baseline and at one or more post-treatment tumor assessment, and no major protocol deviations.

7.5 Application of Analysis Populations

Unless otherwise noted, the analysis populations that will be used for creating the summary table(s) and figures of each type is provided in Table 2. Listing will be provided for all available data.

Table 2: Application of Populations on Tables and Figures

Type	Safety	ITT	CE
Disposition	X		X
Protocol deviations	X		
Demographics	X		
Prior cancer treatment for renal cell carcinoma	X		
Treatment exposure	X		X
Safety evaluations	X		
Efficacy evaluations		X	X

8 STATISTICAL CONSIDERATIONS

All analyses described in this plan are considered a priori analyses in that they have been defined prior to locking the database. All other analyses, if any, designed subsequently to locking the database, will be considered post hoc analyses and will be described as exploratory analyses in the Clinical Study Report.

All summaries and statistical analysis will be performed by SAS v9.3 or later.

8.1 General Statistical Procedures

Frequency distributions for categorical variables will be provided as number of patients with a response in the category and the percentages of the total number of patients in that column. Percentages will be based on number of patients in the given population as noted. Percentages will be reported to one decimal place.

A 2-sided 95% exact binomial (Clopper-Pearson) confidence interval (CI) for categorical variables without multiplicity adjustment will be provided where appropriate for efficacy analysis.

The descriptive statistics for continuous variables will be number of patients, mean, standard deviation (STD), median, minimum and maximum. Mean and median will be reported to 1 more decimal place than the raw data, while the STD will be reported to 2 more decimal places than the raw data. Minimum and maximum will be reported the same as the original data.

In general, all listings will be ordered by study treatment, patient ID and visit for available data unless otherwise specified in the text.

8.2 Patients Disposition

Number of patients who completed the study, are still receiving treatment by the data lock date, and number of patients who discontinued from treatment and primary reasons of discontinuation will be tabulated for Safety Population and CE Population.

Patients' disposition will be provided in a data listing.

8.3 Protocol Deviations

Only major protocol deviation will be collected in the study. Major protocol deviations are defined as those deviations from the study protocol that may have the ability to impact the interpretation of the safety and efficacy results.

Major protocol deviations for all parts of the study include (but are not limited to):

- Received study treatment without meeting eligibility criteria (unless a specific waiver was issued prior to first dose)
- Received wrong treatment or incorrect dose

- Failure to collect data necessary to determine the safety/tolerability of X4P-001
- Received excluded concomitant treatment
- Met withdrawal criteria and was not withdrawn by the site PI nor discussed with the Medical Monitor

If a reported protocol deviation does not meet classification criteria for major deviation, the protocol deviation will be reported as a protocol deviation without a classification.

All protocol deviations will be identified and finalized prior to database lock and documented.

Number and percentage of patients with a major protocol deviation will be tabulated for Safety Population.

Protocol deviations will be listed.

8.4 Demographics and Baseline Characteristics

8.4.1 Demographics and Baseline Characteristics

Demographic and baseline parameters will be tabulated using descriptive statistics for Safety Population. The following variables will be included in the summary table:

- Age (years), calculated as (date of screening - date of birth) / 365.25
- Age category (18 to < 65, ≥ 65 and missing)
- Sex
- Race
- Ethnicity
- Height (cm)
- Screening weight (kg)
- Screening ECOG status

Demographics and baseline characteristics will be listed.

8.4.2 Serology Tests

Blood samples will be collected for analysis of the following: Hepatitis B surface antigen and antibody to hepatitis C virus. Serology tests will be listed only.

8.4.3 Medical History

Medical history will be coded according to the current version of the Medical Dictionary for Regulatory Activities (MedDRA) dictionary version in effect at the time of database freeze.

Medical history data will be listed only.

8.4.4 Prior Cancer Treatment/Procedures for Renal Cell Carcinoma

Prior anticancer treatment and procedures for renal cell carcinoma will be tabulated for Safety Population including:

- Any prior systemic treatment for renal carcinoma (include nivolumab treatment)
- Number of prior systemic treatments for renal cell carcinoma (include nivolumab treatment)
- Duration on last nivolumab monotherapy (months)
- Response on last nivolumab monotherapy before entering study
- Best response to nivolumab
- Any prior procedures

Duration of last nivolumab monotherapy in months is calculated as (date of last nivolumab treatment - date of first nivolumab treatment)/30.4375 for patients' last nivolumab monotherapy.

A data listing of prior anticancer treatment and procedures will be provided.

8.4.5 Prior and Concomitant Medication

All medications as documented by the investigator will be coded using Anatomical Therapeutic Chemical (ATC) classification based on the World Health Organization (WHO) Drug Dictionary (WHO-DD March 2016).

Prior and concomitant medications will be listed only.

8.4.6 Prognosis Factors

Patients survival status before entering the study will be classified into three groups: poor (Heng score ≥ 3), intermediate (Heng score =1 or 2), and favorable prognosis (Heng score=0) [Daniel Y.C. H 2009]. Prognosis will be summarized for Safety Population, ITT and CE Populations, and a detailed listing will be provided.

8.5 Safety Analysis

8.5.1 Adverse Events

AEs will be coded using MedDRA v19.0 or later and will be classified by SOC and PT of MedDRA. Severity of AEs will be assessed by investigators according to CTCAE (v4.03).

Related AEs are defined as possibly related or related to study drug as assessed by the Investigator, or with missing relationship.

A separate listing of details of any deaths will also be presented.

An overall AE summary will be presented for the following categories:

- Any TEAEs
- Drug-related TEAEs
  - Any X4P-001 related TEAEs
  - Any Nivolumab related TEAEs
  - Any X4P-001 or Nivolumab related TEAEs
- Any Grade $\geq$ 3 TEAEs
- Any drug-related Grade $\geq$ 3 TEAEs
  - Any X4P-001 related Grade $\geq$ 3 TEAEs
  - Any Nivolumab related Grade $\geq$ 3 TEAEs
  - Any X4P-001 or Nivolumab related Grade $\geq$ 3 TEAEs
- Any TEAEs leading to death
- Any drug-related TEAEs leading to death
  - Any X4P-001 related TEAEs leading to death
  - Any Nivolumab related TEAEs leading to death
  - Any X4P-001 or Nivolumab related TEAEs leading to death
- Any SAE
- Any drug-related SAEs
  - Any X4P-001 related SAEs
  - Any Nivolumab related SAEs
  - Any X4P-001 or Nivolumab related SAEs
- Any TEAEs leading to study drug discontinuations
  - Any TEAEs leading to X4P-001 discontinuations
  - Any TEAEs leading to Nivolumab discontinuations
  - Any TEAEs leading to X4P-001 or Nivolumab discontinuations
- Any drug related TEAEs leading to study drug discontinuation
  - Any drug-related TEAEs leading to X4P-001discontinuation
  - Any drug-related TEAEs leading to Nivolumab discontinuation
  - Any drug-related TEAEs leading to X4P-001 or Nivolumab discontinuation
- Any TLTs occurring during cycle 1

Both number of events and number of patients will be tabulated. For patients, percentages will be calculated from the total number of patients per dose group.

Summaries of TEAEs by System Organ Class (SOC) and preferred term sorted by decreasing frequency of preferred term within SOC include the following:

- TEAEs
- Drug-related TEAEs
- SAEs

- Drug-related SAEs
- TEAEs leading to discontinuation of either study drug
- TEAEs leading to death
- TEAEs leading to X4P-001 dose interruption
- TLTs occurring during cycle 1

Both number of events and number of patients will be tabulated. For patients, percentages will be calculated from the total number of patients per dose group.

A summary of TEAEs by SOC, preferred term and maximum severity, sorted by decreasing frequency of preferred term within SOC, will also be provided for:

- TEAEs
- TEAEs with CTCAE Grade $\geq$ 3 split by maximum grade and overall
- Drug-related TEAEs with CTCAE Grade $\geq$ 3 split by maximum grade and overall

Summaries of TEAEs by decreasing frequency of preferred term will be presented for:

- All TEAEs
- SAEs
- Most Frequent TEAEs (>10%)
- CTCAE Grade $\geq$ 3 TEAEs
- Drug-related TEAEs
- Drug-related SAEs
- Drug-related CTCAE Grade $\geq$ 3 TEAEs

The following listing will be provided:

- All AEs (flagging those that are treatment emergent)
- Related AEs (flagging those related to X4P-001, related to nivolumab or both)
- Serious adverse events (SAEs)
- AEs leading to discontinuation (flagging those leading to discontinuation of X4P-001, nivolumab or both)
- AEs leading to death
- TLTs

8.5.2 Treatment Exposure

Details of X4P-001 and nivolumab administration will be listed. This will include details of drug administration, treatment dispensed and returned, and the frequency and timing of any dose modifications.

Exposure to X4P-001 will be summarized using the following parameters for the Safety Population and CE Population:

- Time on treatment (months) defined as

  (Last dose date of X4P-001 – first dose date X4P-001 +1)/30.4375

- Actual time on treatment (months) defined as

  (Total time on treatment (days) – number of days of X4P-001 dose interruptions)/30.4375

Dose modification for X4P-001 including number and percentage of patients with any, 1, 2 and 3 or more dose increases, dose decreases, dose holds and dose modifications (increases or decreases) will be presented for the Safety Population and CE Population.

Details of study treatment exposure will be listed.

8.5.3 Clinical Laboratory Tests

All laboratory parameters collected at each center's local laboratory will be normalized by converting values in original units to values in SI units and classified as normal, low, or high based on normal ranges supplied by the local laboratories and upon employing standardization.

For hematology, chemistry, coagulation and thyroid function laboratory parameters which are normalized in SI units, descriptive summary tables for observed values and changes from baseline will be provided by study treatment and visit for Safety Population.

Laboratory values will also be categorized according to their NCI-CTCAE (V4.03) toxicity grade. For applicable parameters, shift tables will be presented from the baseline toxicity grade to the worst post-baseline visit value (scheduled or unscheduled).

For Non-NCI-CTC clinical chemistry and hematology laboratory parameters, shift tables of normal, abnormal NCS and abnormal CS results will be presented from the baseline value to the worst post-baseline visit value (scheduled or unscheduled).

Separate listings will be provided for all laboratory tests including urinalysis and pregnancy testing.

8.5.4 Physical Examination Findings

Physical examination will be presented in listing visit.

8.5.5 Ophthalmologic Examination

Ophthalmologic examination will be performed throughout the study. Details of ophthalmologic results by local review will be listed. Shift tables of normal, abnormal NCS and abnormal CS results will be presented from baseline to the worst post-baseline visit value (scheduled or unscheduled).

8.5.6 Vital Signs

Vitals signs will be collected throughout the study. The value and change from baseline for vital sign parameters will be listed and summarized descriptively for each scheduled time-point during the study.

8.5.7 ECOG performance status

Details of ECOG performance status will be listed.

8.5.8 Electrocardiogram (ECG)

ECG data will be collected by using a digital 12-lead ECG machine throughout the study.

The value and change from baseline in ECG parameters (heart rate, RR, PR, QRS, QT and QTc) will be listed and summarized descriptively for each scheduled time-point during the study. RR interval in seconds is calculated as 60 divided by HR in beats/min. Both QTcB and QTcF may be collected and these will be summarized separately, deriving these if they are not collected for a patient, using the following equations:

- $QTcB=QT/\sqrt{RR}$
- $QTcF=QT/\sqrt[3]{RR}$

For QTcB and QTcF, tables will be presented to indicate the number of patients by visit with values ≥ 450 msec, ≥ 480 msec, ≥ 500 msec, an increase from baseline >30 msec and an increase from baseline >60msec.

ECG data will be listed.

8.6 Efficacy Analysis

Tumor response assessments will be conducted every eight (8) weeks for 80 weeks (20 cycles) and then every 12 weeks thereafter, at End of Treatment, and as indicated based on new signs, symptoms or laboratory findings.

8.6.1 RECIST v1.1 Based Assessment

Imaging will be interpreted using RECIST v1.1. Tumor response including both confirmed and unconfirmed ORR and DCR will be tabulated using best overall response, incorporating 95% exact Clopper-Pearson confidence intervals for both ITT Population and CE Population.

For confirmed responses, responses must be confirmed at least 28 days after the original response. A visit after 2 missed visits will not be considered a confirmation visit. A response of PR followed by a response of CR will be considered as a confirmed PR if there is no subsequent CR.

In addition, the following plots will be provided for both ITT Population and CE Population:

- Waterfall plots of the best percentage change in tumor size (i.e. maximum tumor reduction, or minimum increase in the absence of any reduction)
- Spider plots of the percentage change from baseline in the sum of diameters over time connected with a line
- Swim lane plots of time on study treatment and on prior nivolumab treatment with symbols indicating response start, progression, and withdrawal from study, where applicable.

Details of target lesions, non-target lesions, new lesions and overall tumor response will be listed. A by-patient listing will also be provided for duration of study treatment and prior nivolumab treatment.

8.6.2 iRECIST Based Assessment

iRECIST data will not be available due to the early termination of the study. Tumor response assessments will not be explored using iRECIST criteria.

8.7 Pharmacokinetic Analysis

Plasma or serum concentrations and pharmacokinetic parameters will be not summarized in this SAP.

8.8 Pharmacodynamic Analysis

Pharmacodynamic data will be listed only.

9 References

Daniel Y.C. H, Wanling X, Meredith M. R, et al. Prognostic Factors for Overall Survival in Patients with Metastatic Renal Cell Carcinoma Treated with Vascular Endothelial Growth Factor–Targeted Agents: Results from a Large, Multicenter Study. Journal of Clinical Oncology. 2009; 27:34-39.