This study will be conducted according to the protocol and in compliance with Good Clinical Practice, the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements.

Study Title:	A Phase 1b/2a Trial Adding X4P-001 in Patients Receiving Nivolumab for Treatment of Advanced Clear Cell Renal Cell Carcinoma
Investigational Drug:	X4P-001
IND #:	124194
ClinicalTrials.gov ID	NCT02923531
Sponsor:	X4 Pharmaceuticals, Inc. 955 Massachusetts Ave, 4th Floor Cambridge, MA 02139
Protocol Number:	X4P-001-RCCB
Protocol Version, Date:	3.0 (05 Jul 2017)
Replaces Version, Date:	2.0 (20 Feb 2017)

INVESTIGATOR STATEMENT

I understand that all documentation provided to me by X4 Pharmaceuticals, Inc. (X4), or its designated representative(s) concerning this study that has not been published previously will be kept in the strictest confidence. This documentation includes the study protocol, investigator brochure, case report forms, and other scientific data.

This study will not commence without the prior written approval of a properly constituted Institutional Review Board/Independent Ethics Committee (IRB/IEC). No changes will be made to the study protocol without the prior written approval of X4 and the IRB/IEC, except where necessary to eliminate an immediate hazard to the patient.

Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with all of the instructions and procedures found in this protocol and to give access to all relevant data and records to X4 as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform X4 immediately that this request has been made.

I have read, understood, and agree to abide by all the conditions and instructions contained in this protocol.

Investigator Signature	Date
Printed Name	

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LIST OF TABLES IN THE TEXT

LIST OF ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse event
ALC	Absolute lymphocyte count
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the concentration-versus-time curve
BID	Twice daily
BP	Blood pressure
ccRCC	Clear cell renal cell carcinoma
CE	Clinically Evaluable
CI	Confidence interval
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CNS	Central nervous system
CR	Complete response
CRA	Clinical research associate
CRO	Contract research organization
CS	Clinically significant
CSR	Clinical Study Report
CT	Computed tomography
CV	Coefficient of variation
CXCL12	C-X-C chemokine ligand type 12 (also designated SDF-1)
CXCR4	C-X-C chemokine receptor type 4
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DCR	Disease control rate
DRC	Data Review Committee
EC_{50}	Half-maximal effective concentration
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form

Abbreviation	Explanation
EDC	Electronic data capture
EHR	Electronic health records
E_{max}	Maximum exposure
EOS	End-of-study
EOT	End-of-treatment
FDA	Food and Drug Administration (US)
FFPE	Formalin fixed paraffin embedded
FGFR	Fibroblast growth factor receptor
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
Ig	Immunoglobin
IND	Investigational New Drug Application
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
kit	Cytokine receptor
LFT	Liver function tests
MDSC	Myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
mTOR	Mechanistic target of Rapamycin
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCS	Not clinically significant

Abbreviation	Explanation
NOAEL	No observed adverse effect level
ORR	Overall response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PD-L2	Programmed death-ligand 2
PE	Physical Exam
PFS	Progression-free survival
PDGFR	Platelet-derived growth factor receptor
PHB	*p*-hydroxybenzoate salt
PHI	Protected health information
PK	Pharmacokinetics
PO	By mouth
PR	Partial response
QD	Once daily
RCC	Renal cell carcinoma
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Stable disease
SDF-1	Stromal-derived-factor 1 (also designated CXCL12)
SOD	Sum of diameters
SUSAR	Suspected unexpected serious adverse reaction
$T_{1/2}$	Half-life
TBIL	Total bilirubin
TKI	Tyrosine kinase inhibitor
TLT	Treatment-limiting toxicity
T_{max}	Time to maximum concentration
TME	Tumor microenvironment

Abbreviation	Explanation
TMF	Trial master file
Treg	T regulatory
TTP	Time to progression
ULN	Upper limit of normal
US	United States
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
WBC	White blood cell
WOCP	Women of childbearing potential

PROTOCOL SUMMARY

Study title	A Phase 1b/2a Trial Adding X4P-001 in Patients Receiving Nivolumab for Treatment of Advanced Clear Cell Renal Cell Carcinoma
Study number	X4P-001-RCCB
Sponsor	X4 Pharmaceuticals, Inc. 955 Massachusetts Ave, 4th Floor Cambridge, MA 02139
Phase	1b/2a
Study centers / countries	Multiple Centers in the United States (US).
Planned study period	First patient enrolled: Q1 2017 Last patient enrolled: Q4 2017 Last patient last visit: Q2 2018
Study objectives	The primary objective is: • To characterize the safety and tolerability of X4P-001 used in combination with nivolumab in patients tolerating nivolumab but not exhibiting radiologic response. Secondary objectives are: • 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. The exploratory objectives are: • 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 Tumours for immune-based therapeutics (iRECIST) [Seymour 2017].
Study design and plan	This single-arm, open-label, multi-center study is designed to characterize the safety and tolerability of adding X4P-001 to nivolumab treatment in patients with advanced clear cell renal cell carcinoma (ccRCC). To be eligible, patients must have received nivolumab and have demonstrated a confirmed best response of stable disease (SD) or radiologic progression (PD) without clinical deterioration, as assessed by their Investigator. Confirmed SD or confirmed PD refers to a response that is confirmed by a 2nd scan which is at least 4 weeks apart from the previous scan. 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. • Progressive disease (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 the Response Evaluation Criteria for Solid Tumors, version 1.1 (RECIST v1.1) [Eisenhauer 2009], 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 the study regimen; 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 [Seymour 2017] must discontinue study treatment. After the first 3 patients complete 28 days of combination treatment (Cycle 1), a Data Review Committee (DRC) will review all available safety data and make a recommendation on the progress of the study. To further protect patients' safety, TLTs will continue to be monitored during the remainder of the study. If excessive TLTs are observed anytime during the trial, a dose de-escalation can be enforced following DRC review or the trial can be stopped at the sponsor's discretion. Specifically, if less than or equal to 4 TLTs are observed in the first 12 patients, the trial will continue with the same dose level for the remaining patients. If 5 or more TLTs are observed, the trial may continue with dose de-escalation, i.e., the rest of the patients will be dosed at 200 mg QD. With the de-escalation rule, the trial with a higher TLT rate at the starting dose (400 mg QD) will increase the probability of the de-escalation to

	protect patients' safety. For instance, if the TLT rate in the first 12 patients is 30%, the probability of de-escalation is 28%; if the TLT rate is 40%, the probability of de-escalation is 56%; if the TLT rate is 50%, the probability of de-escalation is 81%.
Planned number of patients	Up to 20 patients are planned to be enrolled.
Schedule of visits and assessments	Patients will be screened for study eligibility within 28 days prior to Day 1 (the first dose of study drug). Eligible patients will be enrolled and start combination study treatment on Cycle 1, Day 1. During treatment, assessments for treatment response (or PD) are scheduled every 8 weeks during the first 12 months of treatment and every 12 weeks thereafter. An End-of-Treatment (EOT) visit will be performed within 6 days after the last dose of study drug or the decision to terminate treatment prematurely. An End-of-Study (EOS) visit (i.e., the final study event) will be performed 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. Provision is made for the Sponsor to analyze the study data after all enrolled patients have completed at least 12 months of treatment. Patients receiving study treatment at that time may continue to receive treatment during an extension phase of the protocol, with an adjusted schedule of assessments and limited central data collection.
Diagnosis and main inclusion criteria	Patients must meet all of the following criteria to be eligible for study participation: 1. Be at least 18 years of age. 2. Have signed the current approved informed consent form. 3. Have a histologically confirmed diagnosis of renal cell carcinoma with a documented clear cell component (i.e., ccRCC). 4. Be currently receiving nivolumab and be considered by their Investigator to have the potential to derive clinical benefit from continuing treatment with nivolumab. 5. Has a best response of confirmed SD or confirmed PD* (based on RECIST v1.1 [Eisenhauer 2009]) on current nivolumab treatment prior to initiation of this study.

	* confirmed SD or confirmed PD refers to a response that is confirmed by a 2nd scan which is at least 4 weeks apart from the previous scan. 6. Have on computed tomography (CT) imaging done within 28 days of Day 1 findings consistent with advanced ccRCC, including at least one extra-renal measurable target lesion meeting the criteria of RECIST v1.1. 7. Agree to use contraception from screening, through the study, and for at least 5 months after the last dose of nivolumab as follows: • For women of childbearing potential (WOCP, see Section 7.4.1.2 for definition) agree to use highly effective contraceptive methods. Acceptable methods are described in Section 7.4.1.3. • For males, agree to use a condom with any WOCP sexual partner. 8. Agrees to permit submission of archived tumor tissue to Sponsor for analysis, if available. 9. Be willing and able to comply with this protocol.

Exclusion criteria	Patients with any of the following will be excluded from participation in the study: 1. Is pregnant or nursing. 2. Has life expectancy of less than 3 months. 3. Has performance status ≥2 (Eastern Cooperative Oncology Group [ECOG] criteria). 4. Has clinically significant and/or uncontrolled heart disease such as congestive heart failure requiring treatment (New York Heart Association Class III or IV), uncontrolled hypertension, or clinically significant arrhythmia. 5. Has previously received X4P-001. 6. Has a second malignancy. Except: malignancies that were treated curatively and have not recurred within 2 years prior to study treatment; completely resected basal cell and squamous cell skin cancers; any malignancy considered to be indolent and that has never required therapy; and completely resected carcinoma in situ of any type. 7. Has active central nervous system (CNS) metastases (including evidence of cerebral edema by MRI, or progression from prior imaging study, or any requirement for steroids, or clinical symptoms of/from CNS metastases) within 28 days prior to study treatment. Subjects with known CNS metastases must have a baseline MRI scan within 28 days of study treatment. 8. Has ongoing clinical adverse events National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade >2 resulting from prior cancer therapies, including nivolumab (except alopecia or hypothyroidism). 9. Has a known history of a positive serology or viral load for human immunodeficiency virus (HIV) or a known history of acquired immunodeficiency disorder. 10. Has had within the past 6 months the occurrence or persistence of one or more of the following medical conditions that could not be controlled with usual medical care (e.g., required emergency care or hospitalization): hypertension, angina, congestive heart failure, diabetes, seizure disorder. 11. Has had within the past 6 months the occurrence of one or more of the following events: myocardial infarction, cerebrovascular accident, deep vein thrombosis, pulmonary embolism, hemorrhage

	(NCI CTCAE Grade 3 or 4), chronic liver disease (meeting criteria for Child-Pugh Class B or C), or organ transplantation. 12. Has had within the 4 weeks prior to initiation of study drug surgery requiring general anesthesia. 13. Has, at screening, serologic laboratory tests meeting one or more of the following criteria: • An indeterminate or positive test for antibody to hepatitis C virus (HCV), unless documented to have no detectable viral load on two independent samples. • A positive test for hepatitis B surface antigen (HBsAg). 14. Has, at screening, safety laboratory tests meeting one or more of the following criteria: • Hemoglobin <8.0 g/dL (transfusion is allowed) • Absolute neutrophil count (ANC) <1,500/µL • Platelets <75,000/µL • Creatinine >2.0x upper limit of normal (ULN) • Serum aspartate transaminase (AST) or alanine transaminase (ALT) >2.5x ULN o AST and ALT >5x ULN for patients with liver metastasis • Total bilirubin >1.5x ULN (unless due to Gilbert's Syndrome, total bilirubin > 3.0x ULN and direct bilirubin > 1.5x ULN) • International normalized ratio (INR) >1.5x ULN 15. Has, within 4 weeks prior to Day 1, received systemic corticosteroids exceeding prednisone 10 mg per day (or equivalent). Topical, inhaled, nasal and ophthalmic steroids are allowed; for other immunosuppressive agents, the exclusionary dose and duration will be determined in consultation with the Medical Monitor. 16. Has, within three (3) weeks prior to Day 1, received anti-cancer therapy other than nivolumab, including a tyrosine kinase inhibitor (TKI), bevacizumab, chemotherapy (e.g., mitomycin-C, nitrosourea), immunotherapy, or radiation therapy. For investigational anti-cancer therapies, the interval will be determined in consultation with the Medical Monitor.

	17. Has, within 2 weeks prior to Day 1, received a medication prohibited based on cytochrome P450 (CYP) 3A4 interaction. 18. Has, at the planned initiation of study drug, an uncontrolled infection. 19. Has any other medical or personal condition that, in the opinion of the Investigator, may potentially compromise the safety or compliance of the patient, or may preclude the patient's successful completion of the clinical study.
Investigational Medicinal Product: dose/mode of administration/dosing schedule	All patients will receive the investigational agent X4P-001 in combination with nivolumab (OPDIVO®), a programmed cell death protein 1 (PD-1) blocking antibody approved for the treatment of patients with advanced ccRCC. X4P-001 will be provided as 100 mg capsules. (Manufacturing of a 200 mg capsule formulation is under development and may be introduced into the clinic when released.) All patients will receive X4P-001 400 mg once daily (QD) orally (PO). X4P-001 is to be administered at a consistent time each morning (±2 hours) with no food or drink (except water) for at least 1 hr pre-dose and continuing for at least 2 hr post-dose. All patients will have received nivolumab as per standard of care prior to enrollment to the study. Enrolled patients will continue treatment with nivolumab at 240 mg every 2 weeks by intravenous (IV) infusion over 60 minutes using a sterile, non-pyrogenic, low protein binding in-line filter with pore size of 0.2 to 1.2 micrometer. Other drugs should not be administered concurrently through the same IV line.
Reference therapy: dose/mode of administration/dosing schedule	None.
Planned treatment duration per patient	Patients are expected to receive study treatment until the earliest of: • TLT event: – For any TLT event occurring in Cycle 1, study treatment will be discontinued permanently. – For TLT events occurring after Cycle 1, provision is made for dose interruption. • PD

Endpoints:	Safety endpoints are: • Adverse events (AEs). • Clinical observations (e.g., vital signs, physical examination). • Laboratory test results (e.g., clinical chemistry, hematology). • Electrocardiogram (ECG) findings. • Ophthalmologic examination findings. Efficacy endpoints are: • Objective response rate (ORR), where response is defined as achieving either complete response (CR) or partial response (PR). • Time to objective response. • Duration of objective response. • Disease control rate (DCR; CR+PR+SD). • Progression-free survival (PFS), defined as the time from first administration of combination regimen until objective tumor progression or death from any cause. • Time to progression (TTP), defined as the time from first administration of combination regimen until objective tumor progression. PK endpoints are: • Area under the concentration-versus-time-curve (AUC). • Maximum concentration (C_{max}). • Time to reach maximum concentration (T_{max}). Exploratory endpoints are: • Effect of study treatment on white blood cell counts (WBCs), including ANC and absolute lymphocyte counts (ALC), in blood. • Effect of study treatment on treatment- and tumor-related biomarkers in peripheral blood mononuclear cells (PBMCs), including T regulatory (Treg) lymphocytes, activated T cells, and myeloid-derived suppressor cells (MDSCs), and in serum, including CXCL12. • Effect of study treatment on exploratory biomarkers in tumor tissue.

	• Efficacy endpoints may be explored using the iRECIST assessment.
Statistical methods (includes sample size calculation)	**Sample Size:** 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.
	Statistical Methods: The primary objective of the study is safety and tolerability. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 16.0 (or later) and tabulated by system organ class and preferred term, severity, and relationship to study therapy. Laboratory results, vital signs, ECOG performance status, and ECG parameters will be summarized using descriptive statistics. Laboratory values will also be graded according to the NCI CTCAE, Version 4.03, and summarized in shift tables. TLT events will be summarized descriptively. All safety data will be presented in listings. Best response per RECIST v1.1 and ORR will be summarized. Patients who do not have data sufficient for response assessment will be considered treatment failures. The number and proportions of responders will be summarized as a percent of the analysis population. The Intent-to-Treat (ITT) will be the primary population for analysis and the clinically evaluable (CE) population will be considered supportive. The DCR will be calculated as the number of patients who had CR, PR, or SD divided by the ITT population. PFS, duration of response, and TTP will be summarized using Kaplan Meier methods. Median, 25th, and 75th percentiles will be reported. The 95% confidence intervals on the median and proportion of censored data also will be presented. Further details regarding censoring will be described in the Statistical Analysis Plan (SAP).

	PK data will be analyzed using descriptive statistics for AUC, C_{max}, and T_{max}. Pharmacodynamic data will be analyzed as described in the SAP.
Schedule of events:	The schedule of events is presented in Table 1-1.

Table 1-1: 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. See Section 7.3.1 for events during Extension Phase.
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 (see Section 7.1.1.1).
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; see Section 7.1.4.1 for details.
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 (see Section 7.2.1 for details); performed at local laboratory.
13. Ophthalmologic examination (see Section 7.1.1.5 for details) 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 (see Section 7.4.1.2), 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 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 – see Section 7.1.3.1 for details.
19. Site to confirm availability of archived tumor tissue.
20. Administration of nivolumab – see Section 6.1.5.2 for details.
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 (see Section 7.4.4.1).
24. ECG assessment performed at 2 hr post-dose (± 15 min).

1. KEY ROLES

Study Sponsor:

X4 Pharmaceuticals, Inc.
955 Massachusetts Ave, 4th Floor
Cambridge, MA 02139

Primary Sponsor Contact:

[redacted]
X4 Pharmaceuticals, Inc.
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Sponsor Signatory:

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2. INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1. Background Information

2.1.1. Renal Cell Carcinoma

Renal Cell Carcinoma (RCC) is the most common malignant lesion of the kidney, with an estimated annual incidence in the United States (US) of over 50,000 new cases and 13,000 deaths per year [Siegel 2015; Richie 2006]. With currently available treatments, the median overall survival (OS) is approximately 28 months [Motzer 2013].

Several different classes of therapeutic agents are available for patients with advanced (unresectable) disease. First-line treatment is typically a small molecule tyrosine kinase inhibitor (TKI) targeting the vascular endothelial growth factor receptor (VEGFR) signaling pathway. Additional agents for second-line therapy include anti-VEGF antibodies, mechanistic target of rapamycin [mTOR] inhibitors, as well as agents active against multiple tyrosine kinases. In most studies, these agents reduce tumor size and prolong progression-free survival (PFS), but their impact on OS is less clear. Two agents recently approved by US Food and Drug Administration (FDA), nivolumab (an anti-programmed cell death protein 1 [PD-1] immunotherapy) and cabozantinib (a TKI targeting multiple receptors, including VEGFR and MET) have shown OS benefits relative to mTOR inhibition in patients with prior VEGFR TKI therapy [Nivolumab prescribing information, 2017; Cabozantinib prescribing information, 2016].

2.1.2. Nivolumab in the treatment of RCC

Nonclinical and clinical studies over the past decade have identified critical mechanisms by which cancers subvert normal immunomodulatory mechanisms (referred to as "checkpoints") to block effective anti-tumor immune surveillance. These insights have led to the development of a new class of immunotherapeutics referred to as "checkpoint inhibitors," which include nivolumab, a human immunoglobulin (Ig) G4 monoclonal antibody that binds to PD-1 and blocks its interaction with programmed death-ligand 1 and 2 [PD-L1 and PD-L2], releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response.

Nivolumab [OPDIVO®] was approved in November 2015 by the US FDA for use in patients with advanced RCC who have received prior anti-angiogenic therapy [Nivolumab prescribing information, 2017]. The approval was based on a randomized (1:1) open-label study of nivolumab versus everolimus, an mTOR inhibitor indicated for the treatment of patients with advanced RCC after failure of sunitinib or sorafenib. Nivolumab demonstrated a statistically significant improvement in OS compared to everolimus, with a median survival of 25.0 vs. 19.6 months (hazard ratio 0.73, $p<0.002$) and confirmed objective response rates (ORR) of 21.5% vs 3.9%, respectively.

However, despite the improvements in OS and ORR, no difference was observed in overall progression-free survival [Motzer 2015]. Many patients demonstrated initial periods of stable disease (SD) or radiologic progression without clinical deterioration, but did not experience sustained benefit, including approximately 35% of patients whose best response to treatment was progressive disease (PD). Thus, there remains an unmet need for agents that improve outcomes by increasing early response rate or by preventing or delaying treatment resistance, translating into additional increases in OS.

2.1.3. CXCR4 (C-X-C Chemokine Receptor Type 4)

CXCR4 (C-X-C chemokine receptor type 4) is the receptor for CXCL12 (C-X-C chemokine ligand type 12; also referred to as SDF-1α, stromal-derived-factor 1α). CXCL12 has potent chemotactic activity for lymphocytes and myeloid-derived suppressor cells (MDSCs), and is important in controlling the trafficking of both hematopoietic stem cells and endothelial progenitor cells. CXCR4 is also expressed and active on multiple types of human cancers, including clear cell renal cell carcinoma (ccRCC), ovarian cancer, and melanoma, and increased expression of CXCR4 on tumor cells has been associated with significantly decreased OS [Staller 2003; Sekiya 2012; Ehtesham 2008; Maréchal 2009].

In murine cancer models interference with CXCR4 function has been demonstrated to disrupt the tumor microenvironment (TME) and unmask the tumor to immune attack by multiple mechanisms, including:

- Decreasing the infiltration of MDSCs [Obermajer 2011; Gil 2014; Panka 2016]
- Increasing the ratio of CD8+ T cells to T regulatory (Treg) cells [Righi 2011; Feig 2013; Fearon 2014]
- Eliminating tumor re-vascularization [Righi 2011; Fearon 2014]

These effects result in significantly decreased tumor burden and increased overall survival in xenograft, syngeneic, as well as transgenic, cancer models [Righi 2011; Feig 2013; Kioi 2010].

We postulate that effective CXCR4 antagonism by X4P-001 would be of potential benefit in patients with advanced ccRCC and other cancers by multiple mechanisms:

- Decreased recruitment of MDSC, resulting in increased anti-tumor immune attack.
- Sustained decrease in neoangiogenesis and tumor vascular supply.
- Interference with the autocrine effect of increased expression by ccRCC of both CXCR4 and CXCL12, its only ligand, thereby, potentially reducing cancer cell metastasis.

This clinical study in patients with advanced ccRCC will evaluate the addition of X4P-001 in patients who are receiving nivolumab and have not achieved a radiologic response. We hypothesize that the combination has the potential to improve outcomes by further enhancing antitumor immune activity.

2.2. Overview of X4P-001

X4P-001 is a potent, orally bioavailable CXCR4 antagonist [Stone 2007], that has demonstrated activity in solid and liquid tumor models [Parameswaran 2011, and unpublished data]. We postulate that effective CXCR4 antagonism by X4P-001 would be of potential benefit in patients with advanced ccRCC and other cancers by multiple mechanisms:

- Decreased recruitment of MDSC, resulting in increased anti-tumor immune attack.
- Sustained decrease in neoangiogenesis and tumor vascular supply.
- Interference with the autocrine effect of increased expression by ccRCC of both CXCR4 and CXCL12, its only ligand, thereby, potentially reducing cancer cell metastasis.

This clinical study in patients with advanced ccRCC will evaluate the addition of X4P-001 in patients who are receiving nivolumab and have not achieved a radiologic response. We hypothesize that the combination has the potential to improve outcomes by further enhancing antitumor immune activity.

X4P-001 was previously under development for the treatment of HIV infection based on the role of CXCR4 in viral entry into the cell. That program, which is presented in detail in the Investigator Brochure, included nonclinical toxicology studies and clinical studies using the free base formulation, then designated AMD11070 and here X4P-001. Throughout the prior clinical development program, the drug product used was capsules containing 100 mg of the free base. The same formulation will be used in this protocol (see Section 6.1.2.1).

Concurrent pharmaceutical development work identified the *p*-hydroxybenzoate salt (PHB) salt form of the drug (designated AMD11070PHB) for future manufacturing and development purposes. Animal toxicology studies (13- and 26-week duration) conducted with AMD11070PHB demonstrated unexpected findings, including retinal changes in albino rats treated for 26 weeks and notable gastrointestinal (GI) intolerance and liver changes in Beagle dogs treated for 13 weeks (see Investigator's Brochure).

Although AMD11070PHB was never administered to humans and is not proposed for use in any clinical studies in this program, these observations were carefully considered in the safety monitoring plans for clinical studies of X4P‑001.

2.2.1. Prior Clinical Studies Conducted Using X4P-001

There are no prior clinical studies of X4P-001 in patients with advanced ccRCC or any other malignancy.

The 4 clinical studies conducted under the prior development program included Phase 1 and 2a studies involved a total of 55 healthy volunteers [Cao 2008; Nyunt 2008] and 16 HIV-infected patients [Moyle 2009; ACTG (DIAIDS) Protocol A5210]. Table 2-1 shows the protocol numbers, titles, and related publications; Table 2-2 summarizes the study populations, objectives, numbers, dose administered, and duration.

These studies demonstrated the following:

- Oral administration of up to 400 mg BID for 3.5 days (healthy volunteers) and 200 mg BID for 8-10 days (healthy volunteers and HIV patients) was generally safe and well-tolerated with no pattern of AEs or clinically significant laboratory changes.
- Oral administration of 200 mg BID and 400 mg once daily (QD) demonstrate the consistent $T_{1/2}$ of 23 hours for X4P-001, supporting the use of QD dosing (see Investigator's Brochure).
- Pharmacodynamic activity, as assessed by increases in circulating WBC, was related to dose and duration of treatment.

Table 2-1: Prior Clinical Studies Conducted using X4P-001 – Protocol Number, Study Title, and Publication[1]

Protocol No.	Study Title	Publications
ACTG A5191	A Phase I, Dose-Rising Study of AMD11070 In HIV-Seronegative Men To Assess the Safety and Pharmacokinetics After Single or Multiple Doses	Stone 2007
AMD-1001 (XACT)	Multicenter, dose-finding safety and activity study of AMD11070 in HIV-infected patients carrying X4-tropic virus	Moyle 2009
AMD-1002 (XIST)	A Study of the Pharmacokinetic Interaction between AMD11070 and Substrates of CYP 3A4 and 2D6 Enzymes in Healthy Volunteers	Nyunt 2008
ACTG A5210	Phase IB/IIA Dose-Finding Safety and Activity Study of AMD11070 (An Orally Administered CXCR4 Entry Inhibitor) in HIV-Infected Subjects	(unpublished)

1. All studies were conducted between 3 Sep 2003 and 13 Jul 2006.

Table 2-2: Prior Clinical Studies Conducted using X4P-001 – Study Population, Objectives, and Exposures

Study ID	Study Population	Study Objective	Cohort (A5191 only)	N	Gender M/F[2]	Dose & Regimen (All oral)	Duration
A5191[1]	Healthy Volunteers	Dose escalation: Safety, PK	A-D	12[1]	43 M, 0 F[a]	Single Dose 50 to 400 mg	1 day
			F, G, I	18[1]		100 to 400 mg, BID	3.5 days (7 doses)
		Effect of food, of ritonavir	H, J, K	32[1]		≤3 doses, 200 mg or 400 mg each	≤3 doses over 6 to 17 days
A5210	HIV-infected	Safety Viral load reduction		6	3 M, 3 F	200 mg, BID	10 days
AMD-1001	HIV-infected	Safety Viral load reduction		10	9 M, 1 F	100 mg, BID (N=2) 200 mg, BID (N=8)	10 days
AMD-1002	Healthy Volunteers	Safety Drug-drug interaction		12	9 M, 3 F	200 mg, BID	8 days

1. Study A5191 enrolled 10 cohorts totaling 68 subjects representing 43 unique individuals. There were 3 subjects in each of the 4 single dose escalation cohorts (A-D) and 6 subjects in each of the 3 multiple dose escalation cohorts (F, G, I). No subject was enrolled in more than one of the dose escalation cohort.
2. Within each study the median age was ~40 years; overall age range was 19 to 58 years.

2.2.2. Clinical Pharmacology of X4P-001

2.2.2.1. Clinical Pharmacokinetics

In the 4 previous clinical studies conducted by AnorMed and NIH (Studies AMD1001, AMD1002, A5191, and A5210) using the freebase formulation in normal healthy volunteers and patients with HIV. Drug was administered PO in all studies; multiple dose studies were conducted using BID dosing. In single and multiple dose escalation studies, maximum concentration (C_{max}) and AUC increased more than dose-proportionally over 50 - 400 mg dose range. Mean terminal half-life ($T_{1/2}$) was 22.9 hr, supporting the QD dosing regimen.

Steady-state PK parameters were similar in healthy volunteers (AMD-1002) and in HIV infected patients (A5210 and AMD-1001). The results (mean ± SD) were derived from 26 subjects, including both healthy volunteers and HIV-infected subjects, who received X4P-001 at 200 mg BID for 8 to 10 days.

- $AUC_{(0\text{-}12hr)}$: 3735 ± 1755 ng·hr/mL
- C_{max}: 1223 ± 600 ng/mL
- Minimum concentration (C_{min}) at 12 hours: 74.3 ± 47.3 ng/mL
- Time to maximum concentration (T_{max}): 2.2 ± 0.9 hr

For 13 subjects, daily $C_{min(trough)}$ concentrations were determined. Overall, subjects reached steady state by Day 6, which is consistent with the $T_{1/2}$ of ~23 hr. Further, C_{min} and $AUC_{(0-12)}$ were strongly correlated suggesting that monitoring C_{min} may provide a practical means for assessing drug exposure.

X4P-001-REGA study was a phase I study in 15 healthy volunteers comparing two different dosing regimens: 200 mg BID and 400 mg QD (10-day treatment). The study was prematurely discontinued on Day 3 due to an insufficient number of patients remaining on the trial to assess the statistical endpoints. In this study, PK samples were collected from 0-12 hr for BID dosing and 0-24 hr for QD dosing. Preliminary PK results are listed below.

Following administration of X4P-001 200 mg BID and 400 mg QD on Day 1, the mean C_{max} were 1070 ng/mL and 2662 ng/mL, respectively; the median T_{max} were 2.5 hr and 1.5 hr respectively. AUC_{0-12} was 3682 ng*hr/mL after 200 mg BID dose and AUC_{0-24} was 9421 ng*hr/mL after 400 mg QD dose. Comparing with results from Study A5191, the exposure in REGA study is higher.

2.2.2.2. Effect of Food on Absorption

In a food-effect study (A5191), 9 male subjects received X4P-001 in the fasted stated (fasting overnight after midnight until 2 hours post-dose) and in the fed state (low-fat meal within 30 minutes prior to dosing), food had a significant negative effect on the bioavailability of X4P-001. C_{max} and AUC_{0-12} in the fed state was 0.33x and 0.44x of that observed in the fasted state, respectively. T_{max} was delayed from 1 hr (fasted) to 3 hr (fed). $T_{1/2}$ was not changed.

See Section 6.1.5.1 for details of food restrictions with oral administration of X4P-001 in this protocol.

2.2.2.3. Potential for Drug-Drug Interactions Based on CYP Metabolism

Two clinical studies (A5191, AMD-1002) were conducted to assess the potential for drug-drug interactions (DDI). Ritonavir (a strong CYP3A4 inhibitor, P-gp inhibitor) resulted in a modest increase in X4P-001 plasma concentrations [A5191, Cao 2008]. The mean C_{max} and AUC of X4P-001 coadministered with the first dose of ritonavir were increased by 39% and 60%, respectively, compared to the administration of X4P-001 alone. Similar effects were seen after ritonavir had been administered twice daily for 14 days.

Study AMD-1002 assessed the effect of X4P-001 on metabolism of CYP3A4 and CYP2D6 substrates, using midazolam and dextromethorphan as substrates [Nyunt 2008]. Administration of X4P-001 had the following effects.

- The C_{max} for midazolam (a CYP3A4 substrate) was unaffected; AUC was 1.33x baseline.
- The C_{max} for dextromethorphan (a CYP2D6 substrate) was 2.5x baseline; the AUC, 2.86x.

The magnitude of the midazolam interaction was modest. The magnitude of the effect on dextromethorphan has significant potential to result in changes in clinical drug response,

affecting either efficacy or toxicity. The clinical study protocols include detailed restrictions on concomitant medications to minimize the potential for drug-drug interactions.

2.2.2.4. Clinical Pharmacodynamics

A primary pharmacodynamic effect of CXCR4 antagonism is mobilization of WBC (including both myeloid and lymphoid cell lines) from the bone marrow into the peripheral circulation. The relationship between plasma drug levels and concurrent peripheral blood WBC counts was examined in phase 1 studies with dense sampling [Stone 2007]. After dosing, circulating WBC counts increased from baseline in all subjects, peaking between 2 and 4 h following dosing. The distribution of concurrent WBC-fold change from baseline versus drug concentration best fit a sigmoid maximum exposure (E_{max}) model.

- The estimated E_{max} was WBC increase to 2.03x baseline (95% confidence interval [CI], 1.95x to 2.11x).
- The estimated half-maximal effective concentration (EC_{50}) was 39 ng/mL (95% CI, 28 to 50 ng/mL), which is below the observed steady-state $C_{min(12h)}$ for X4P-001 at 200 mg BID, the starting dose in the proposed oncology studies.

2.2.3. Clinical Safety Experience with X4P-001

2.2.3.1. Safety Experience – X4 Pharmaceuticals Clinical Development Program

As of July 05, 2017, the following studies have been initiated or completed:

- X4P-001-RCCA – a study of X4P-001 in combination with axitinib for the treatment of patients with advanced ccRCC.
- X4P-001-RCCB – the study detailed in this protocol.
- X4P-001-MELA – a phase 1b study of X4P-001 alone and in combination with pembrolizumab in patients with advanced melanoma.
- X4P-001-MKKA – a phase 2/3 randomized, double-blind, placebo-controlledtrial of X4P-001 in patients with WHIM (Warts, Hypogammaglobulinemia, Infections and Myelokathexis) Syndrome
- X4P-001-REGA – a phase 1 study in healthy volunteers comparing two different dosing regimens: 200 mg BID versus 400 mg QD.

Please refer to the current Investigator's Brochure for more information related to X4P-001's clinical safety data.

2.2.3.2. Safety Experience – Prior Development Program

A total of 71 individuals were exposed to X4P-001 in 4 prior clinical studies. Across these 4 studies:

- The most common AEs across studies were mild to moderate GI events.

- There were no deaths and no discontinuations due to AEs. Two subjects discontinued for personal reasons after receiving 1 or 2 doses of X4P-001.
- There was one SAE, a grand mal seizure in a subject with a history of epilepsy; there were no events of seizure reported in other subjects. This SAE was the only clinical AE assessed as severe (Grade 3).
- There was one other clinically notable AE. A subject with baseline bradycardia experienced an episode of syncope upon standing rapidly. The episode resolved promptly without lying down. There were no events of syncope reported in other subjects.
- There were no laboratory abnormalities assessed as clinically significant. The primary treatment-related laboratory abnormalities observed were the pharmacologically expected increase in circulating neutrophils and lymphocytes. Treatment-emergent elevation in lipase was observed in one asymptomatic patient; the source of the enzyme (pancreas or salivary glands) was unclear.
- A detailed by-subject analysis of abnormal liver function tests (LFTs) revealed no pattern of treatment-emergent LFT abnormalities suggesting a drug effect.

2.2.4. Treatment Effect of X4P-001 in Prior Clinical Studies

As of July 05, 2017, there are no efficacy data with X4P-001 to report in patients with malignancy (including ccRCC or melanoma).

2.2.5. Nonclinical Toxicity Studies of X4P-001

Pivotal nonclinical toxicity studies were conducted in rats and Beagle dogs with X4P-001 administered orally in divided doses, BID. The no observed adverse effect level (NOAEL) in the 4-week rat study was 125 mg/kg/day. Adverse effects at 250 mg/kg/day included decreases in food consumption, body weight, and reticulocyte counts and minimal bone marrow hypocellularity; all except body weight were resolved following a 14-day recovery period.

The dose levels in the 13-week toxicity study in dogs were 10, 20, 35, and 70 mg/kg/day. Microscopic liver findings of pigment deposition and inflammation were reported in all dose groups and across males and females; these findings were typically assessed as minimal and not associated with histopathologic findings of necrosis or with LFT changes. The NOAEL (<10 mg/kg/day) reflected the finding of an isolated focus of liver necrosis (slight) in a single male animal dosed at 10 mg/kg/day. None of the remaining 11 animals (5 males and 6 females) in the 2 lowest dose groups had other liver-related findings and none, including the male with focal necrosis, had treatment-emergent increases in LFTs.

At the 2 highest dose levels (35 and 70 mg/kg/day), 4 of 12 animals were reported to have microscopic liver changes of multifocal necrosis (minimal to slight), further characterized as single cell necrosis in 2 animals. Two of the 12 animals in those dose groups (both

70 mg/kg/day) showed post-treatment increased alanine aminotransferase (ALT), rising to 1.4x above the upper range of controls in a male with no histologic findings, and to 2.4x in a female with multifocal single cell necrosis (slight). There were no elevations in bilirubin in any animal. One male (35 mg/kg/day) had "focally extensive (moderate)" necrosis and inflammation associated with macroscopic discoloration of the liver; transaminases were normal. On review, this lesion was qualitatively different from the microscopic multifocal lesions in other animals and had a subcapsular location, consistent with being secondary to external trauma.

The original development program of AMD11070 identified an alternative salt form of the drug substance for manufacturing purpose, PHB salt (designated AMD11070PHB). Toxicology studies of AMD11070PHB included unexpected findings of retinal degeneration in Albino rats treated for 26 weeks. This was not seen in Beagles administered either PHB or free base (X4P-001) drug forms for up to 13 weeks. AMD11070PHB was never administered to humans and is not proposed for use in any clinical studies in this program.

2.3. Clinical Experience with Related Compounds

Mozobil® (plerixafor) is the only approved agent that blocks the CXCR4 receptor, which is an injectable drug with a very short half-life, and is approved in combination with granulocyte-colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells (HSCs) to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma and multiple myeloma.

In tumor models in mice the drug has been administered by continuous infusion using subcutaneous osmotic reservoirs. The results of those nonclinical studies indicate that CXCR4 receptor blockade has an anti-tumor treatment effect and thereby support the hypothesis that an orally administered agent such as X4P-001 could have clinical benefit.

2.4. Rationale

The current standard of care treatment paradigm for patients with advanced ccRCC includes a multi-TKI, such as sunitinib, as first-line therapy, followed by an immunotherapy, alternative TKI, or targeted therapy for future therapies. Targeting anti-angiogenesis as a mechanism for blocking tumor growth is known to be effective in ccRCC, with several approved anti-angiogenic agents, such as sunitinib, pazopanib, axitinib, and bevacizumab. Targets of multi-TKIs include angiogenic targets as well as other growth factors, such as VEGFR, platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), and cytokine receptor (kit). Recently, nivolumab, an immune checkpoint inhibitor, was approved as a second-line treatment for patients following prior anti-angiogenic therapy. Nivolumab is an antibody that blocks the interaction of PD-1 on T cells with its ligand, PD-L1, resulting in tumor-reactive CD8+ T cells that can activate a cytotoxic immune response. While an OS benefit was demonstrated with nivolumab treatment, it is unable to induce a tumor response in a majority of patients. Only 21.5% of advanced RCC patients achieved an objective radiological response

[Motzer 2015]. Therefore, it is important to identify additional therapies that could augment the anti-tumor immune activity of checkpoint inhibitors, resulting in an increase in the number of patients able to achieve a durable response to treatment.

It is hypothesized that a TME that favors immune suppression results in resistance to both TKIs, as well as immunotherapies. Animal studies of ccRCC xenografts implicate increased infiltration of MDSCs as a central factor in acquired resistance to VEGF-targeted therapies [Panka 2013] as well as other anti-cancer therapies [Shojaei 2007; Finke 2011]. MDSCs also impair the entry of CD-8+ cytotoxic T cells into the TME and facilitate the entry of Treg cells [Zea 2005; Nagaraj 2007].

CXCL12 (previously designated SDF-1), the sole ligand for CXCR4, is increased in the TME, particularly in ccRCC, where it is produced by the tumor in response to hypoxia in a HIF-dependent manner. Increased CXCL12 is considered important in increasing MDSC trafficking into tumor tissue. This hypothesis is supported by recent murine xenograft models in which X4P-001 antagonism of CXCL12/CXCR4 signaling decreased the number of MDSCs in the TME, and directly inhibited the increase in MDSCs associated with treatment with axitinib, a TKI antagonist.

While checkpoint inhibitors facilitate activation of cytotoxic T cells, the agents do not impact T cell trafficking. Analyses of human tumor biopsy samples indicates that a clinical response to checkpoint inhibitors may be predicted by immune markers, such as the ratio of effector T cells to regulatory T cells, inflammatory gene expression patterns, or the presence of CD8+ T cells in the tumor microenvironment both before and shortly after treatment [McDermott 2016; Ji 2012; Ribas 2015; Tumeh 2014]. In melanoma, response to treatment with an anti-PD-1 blocking antibody (pembrolizumab) was associated with greater numbers of CD8+ T cells at the invasive tumor margin prior to treatment, with those cells then demonstrating increased proliferation and tumor infiltration during the course of treatment [Tumeh 2014].

Nivolumab is currently the only immune checkpoint inhibitor approved in RCC. The addition of X4P-001 treatment is hypothesized to increase the clinical response to nivolumab by decreasing MDSCs and increasing cytotoxic T cells at the tumor, thereby providing an influx of cells that can be further activated by the checkpoint inhibitor. Additionally, CXCR4 has a role in trafficking of endothelial progenitor cells which mediate angiogenesis. RCC is known to be responsive to anti-angiogenic agents, and thus X4P-001 targets a second mechanism of tumor growth inhibition.

3. OBJECTIVES AND PURPOSE

3.1. Primary Objective

The primary objective is:

- 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

Secondary objectives are:

- To characterize the 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

Exploratory objectives are to:

- 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) [Seymour 2017].

4. STUDY DESIGN AND ENDPOINTS

4.1. Description of the Study Design

The primary objective of this single-arm, open-label, multi-center study is to characterize the safety and tolerability of adding X4P-001 to nivolumab treatment in patients with advanced ccRCC. To be eligible, patients must have received nivolumab and have demonstrated a confirmed best response of SD or radiologic progression (PD) without clinical deterioration, as assessed by their Investigator. Confirmed SD or confirmed PD refers to a response that is confirmed by a 2nd scan which is at least 4 weeks apart from the previous scan.

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 (see Section 5.6).
- 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 [Eisenhauer 2009] 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 [Seymour 2017] must discontinue study treatment (see Section 5.7.1).

To protect patients' safety, a Data Review Committee (DRC) will review available safety data and make a recommendation on the progress of the study during study treatment (see Section 8.6.2).

4.1.1. Rationale for the Study Design, Including the Choice of Control Groups

4.1.1.1. Rationale for Study Structure

The open-label study design is consistent with both the study objectives and current principles for the early evaluation of investigational drugs in patients with advanced malignancy. The single dose level of X4P-001 in combination with nivolumab, which is approved for certain patients with advanced ccRCC will enable a focused assessment of the safety and tolerability of a novel combination with the potential to provide improved outcomes by preventing or delaying treatment resistance.

4.1.1.2. Rationale for Treatment Regimen

The proposed dose of X4P-001 (400 mg QD) is selected based on the following experience:

- In prior clinical studies, the same total daily exposure administered as 200 mg BID was (a) pharmacologically active (Section 2.2.2.4) and (b) well-tolerated in 26 healthy volunteers and HIV-infected patients treated for 8 to 10 days (Section 2.2.1), with no treatment-related discontinuations and no pattern of significant laboratory abnormalities.
- In prior dose escalation studies, 400 mg BID was well tolerated for 3.5 days.
- The 400 mg daily dose was generally safe and well tolerated in patients who were in the X4P-001-RCCA study as of November 30, 2016 (Section 2.2.3.1).

$T_{1/2}$ of X4P-001 is ~23 hr, supporting once daily dosing (see Section 2.2.2.1).

4.2. Endpoints

4.2.1. Safety Endpoints

Safety endpoints are:

- AEs.
- Clinical observations (e.g., vital signs, physical examination).
- Laboratory test results (e.g., clinical chemistry, hematology).
- Electrocardiogram (ECG) findings.
- Ophthalmologic examination findings.

4.2.2. Efficacy Endpoints

Efficacy endpoints are:

- ORR, where response is defined as achieving either complete response (CR) or partial response (PR).
- Time to objective response.
- Duration of objective response.
- Disease control rate (DCR; CR+PR+SD)
- PFS, defined as the time from first administration of combination regimen until objective tumor progression or death from any cause.
- Time to progression (TTP), defined as the time from first administration of combination regimen until objective tumor progression.

4.2.3. Pharmacokinetic Endpoints

PK endpoints are:

- AUC.
- C_{max}.
- T_{max}.

4.2.4. Exploratory Endpoints

Exploratory endpoints are:

- Effect of study treatment on WBCs, including absolute neutrophil counts (ANC) and absolute lymphocyte counts (ALC), in blood.
- Effect of study treatment on treatment- and tumor-related biomarkers in peripheral blood mononuclear cells (PBMCs), including Treg lymphocytes, activated T cells, and MDSCs, and in serum, including CXCL12.
- Identification of potential biomarkers that may predict response to combination treatment with X4P-001 and nivolumab.
- Tumor response assessed possibly using the iRECIST.

5. STUDY ENROLLMENT AND WITHDRAWAL

5.1. Inclusion Criteria

Patients must meet all of the following criteria to be eligible for study participation:

1. Be at least 18 years of age.
2. Have signed the current approved informed consent form.
3. Have a histologically confirmed diagnosis of RCC with a documented clear cell component (i.e., ccRCC).
4. Be currently receiving nivolumab and be considered by their Investigator to have the potential to derive clinical benefit from continuing treatment with nivolumab.
5. Has a best response of confirmed SD or confirmed PD* (based on RECIST v1.1 [Eisenhauer 2009]) on current nivolumab treatment prior to initiation of this study.

   * confirmed SD or confirmed PD refers to a response that is confirmed by a 2nd scan which is at least 4 weeks apart from the previous scan.
6. Have on computed tomography (CT) imaging done within 28 days of Day 1 findings consistent with advanced ccRCC, including at least one extra-renal measurable target lesion meeting the criteria of RECIST v1.1 (Section 7.1.4.2).
7. Agree to use contraception from screening, through the study, and for at least 5 months after the last dose of nivolumab as follows:

   - For women of childbearing potential (WOCP, see Section 7.4.1.2 for definition) agree to use highly effective contraceptive methods. Acceptable methods are described in Section 7.4.1.3.
   - For males, agree to use a condom with any WOCP sexual partner.
8. Agrees to permit submission of archived tumor tissue to Sponsor for analysis, if available.
9. Be willing and able to comply with this protocol.

5.2. Exclusion Criteria

Patients meeting any of the following criteria are excluded from study participation:

1. Is pregnant or nursing.
2. Has life expectancy of less than 3 months.
3. Has performance status ≥2 (Eastern Cooperative Oncology Group [ECOG] criteria).
4. Has clinically significant and/or uncontrolled heart disease such as congestive heart failure requiring treatment (New York Heart Association Class III or IV), uncontrolled hypertension, or clinically significant arrhythmia.
5. Has previously received X4P-001.

6. Has a second malignancy. Except: malignancies that were treated curatively and have not recurred within 2 years prior to study treatment; completely resected basal cell and squamous cell skin cancers; any malignancy considered to be indolent and that has never required therapy; and completely resected carcinoma in situ of any type.
7. Has active CNS metastases (including evidence of cerebral edema by MRI, or progression from prior imaging study, or any requirement for steroids, or clinical symptoms of/from CNS metastases) within 28 days prior to study treatment. Subjects with known CNS metastases must have a baseline MRI scan within 28 days of study treatment.
8. Has ongoing clinical adverse events National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade >2 resulting from prior cancer therapies, including nivolumab (except alopecia or hypothyroidism).
9. Has a known history of a positive serology or viral load for HIV or a known history of acquired immunodeficiency disorder.
10. Has had within the past 6 months the occurrence or persistence of one or more of the following medical conditions that could not be controlled with usual medical care (e.g., required emergency care or hospitalization): hypertension, angina, congestive heart failure, diabetes, seizure disorder.
11. Has had within the past 6 months the occurrence of one or more of the following events: myocardial infarction, cerebrovascular accident, deep vein thrombosis, pulmonary embolism, hemorrhage (NCI CTCAE Grade 3 or 4), chronic liver disease (meeting criteria for Child-Pugh Class B or C), or organ transplantation.
12. Has had within the 4 weeks prior to initiation of study drug surgery requiring general anesthesia.
13. Has, at screening, serologic laboratory tests meeting one or more of the following criteria:
    - An indeterminate or positive test for antibody to hepatitis C virus (HCV), unless documented to have no detectable viral load on two independent samples.
    - A positive test for hepatitis B surface antigen (HBsAg).
14. Has, at screening, safety laboratory tests meeting one or more of the following criteria:
    - Hemoglobin <8.0 g/dL (transfusion is allowed)
    - ANC <1,500/µL
    - Platelets <75,000/µL
    - Creatinine >2.0x upper limit of normal (ULN)
    - AST or ALT >2.5x ULN
        - AST and ALT >5x ULN for patients with liver metastasis

- Total bilirubin (TBIL) >1.5x ULN (unless due to Gilbert's Syndrome, total bilirubin > 3.0x ULN and direct bilirubin >1.5x ULN)
- International normalized ratio (INR) >1.5x ULN

15. Has, within 4 weeks prior to Day 1, received systemic corticosteroids exceeding prednisone 10 mg per day (or equivalent). Topical, inhaled, nasal and ophthalmic steroids are allowed; for other immunosuppressive agents, the exclusionary dose and duration will be determined in consultation with the Medical Monitor.
16. Has, within three (3) weeks prior to Day 1, received anti-cancer therapy other than nivolumab, including a TKI, bevacizumab, chemotherapy (e.g., mitomycin-C, nitrosourea), immunotherapy, or radiation therapy. For investigational anti-cancer therapies, the interval will be determined in consultation with the Medical Monitor.
17. Has, within 2 weeks prior to Day 1, received a medication prohibited based on CYP3A4 interaction (see Section 7.4.1.1 for details).
18. Has, at the planned initiation of study drug, an uncontrolled infection.
19. Has any other medical or personal condition that, in the opinion of the Investigator, may potentially compromise the safety or compliance of the patient, or may preclude the patient's successful completion of the clinical study.

Patients taking medications prohibited on the basis of CYP 3A4 interactions (see Section 7.4.1.1), may, after discussion with the prescribing physician, be changed to a functionally equivalent, non-prohibited medication, and, after at least two weeks off the prohibited medication, reassessed for enrollment, including rescreening, if necessary.

5.3. Strategies for Recruitment and Retention

Following receipt of IRB/IEC approval, the Investigator may initiate patient recruitment (see Section 13). To reach an economically and socially diverse population, the study may be announced publicly, including on relevant Internet websites; prior to use, the form and content of such announcements will be submitted to the IRB/IEC for approval (see Section 13).

5.4. Participant Withdrawal or Termination

5.4.1. Reasons for Withdrawal or Termination

To provide for consistent accounting of patient disposition, when study treatment is discontinued in an individual patient for any reason, the Investigator will complete the appropriate electronic case report form (eCRF) and select the primary reason from the following standard categories:

- *TLT event* – see Section 5.6.
- *PD per RECIST v1.1* [Eisenhauer 2009] (see Section 7.1.4.2 for details).
- *Clinical Deterioration*

- *Adverse Event, other than TLT* – This includes any AE (clinical or laboratory; serious or non-serious; regardless of relation to study drug), that represents the reason study drug was discontinued, including:
  - The medical judgment of the Investigator based on the best interests of the patient.
- The patient's request based on any AE.
- *Withdrawal of Consent* – The patient desired to withdraw from further participation in the study in the absence of a clinical issue. If the patient gave a reason for withdrawing (e.g., leaving area), it should be recorded in the eCRF.
- *Lost to Follow-Up* – The patient stopped coming for visits.
- *Study Termination* – by the Sponsor, for any reason.

5.4.2. Handling of Participant Withdrawals or Termination

When study treatment is discontinued for any reason, the End-of-Treatment (EOT) and End-of-Study (EOS) visits will be performed as specified. If a patient cannot be seen, attempts will be made to contact the patient by telephone to inquire about reasons for stopping participation and get updated information on any unresolved AEs.

5.5. Premature Termination or Suspension of Study

The Sponsor reserves the right to terminate the study or particular study center at any time. If the Sponsor or Investigator discovers conditions arising during the study that suggest the study should be halted, then study termination can occur only after appropriate consultation between the Sponsor and Investigators. Conditions that may warrant study or study center termination include, but are not limited to:

- The discovery of any unexpected, significant, or unacceptable risk to the patients enrolled in the study.
- Failure of the Investigator to enter patients at an acceptable rate.
- Insufficient adherence to the protocol requirements.
- A decision on the part of the Sponsor to suspend or discontinue development of study drug.

Should the study be closed prematurely, all study materials (study drug, etc.) must be returned to the Sponsor or designee (or disposed of as directed by the Sponsor or designee).

5.6. Definitions of Treatment-Limiting Toxicity

A TLT event is defined as an adverse event that meets *both* of the following criteria within the first 28 days of treatment (Cycle 1):

a) Is assessed by the Investigator as possibly related or related to study drug (X4P-001) (see Section 8.2.3 for details).

b) Represents one of the following events (grading as defined by the NCI CTCAE; Ver. 4.03) (see Section 8.2.1). Laboratory values should be repeated 48-72 hrs after the initial laboratory report to confirm the results.

Table 5-1: Definitions of TLTs

Toxicity	TLT Criteria
Hematology	Grade 4 Neutropenia lasting more than 7 consecutive days
	Grade 3 or 4 neutropenia with fever (temperature of >38.5°C)
	Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia with bleeding
	Grade 4 anemia
	Grade 4 lymphopenia
Non-hematology events	Any ≥ Grade 3 clinical events or laboratory events, except for the events described below, which are TLTs only if they meet the criteria below.
Gastrointestinal	Grade 3 or 4 nausea, vomiting or diarrhea lasting ≥ 48 hr despite optimal medical management
Hepatobiliary	≥ Grade 2 total bilirubin elevation with ≥ grade 2 ALT/AST elevation
	≥ Grade 3 ALT/AST elevation lasting ≥ 5 days or Grade 4 ALT/AST elevation
Pneumonitis	Grade 2 pneumonitis lasting > 7 days despite optimal treatment
Hypertension	Grade 3 hypertension lasting > 7 days despite optimal treatment
Infection	Grade 3 infection or fever in the absence of neutropenia lasting > 5 days
Electrolytes	Grade 3 electrolyte abnormalities lasting > 7 days
Rash and/or photosensitivity	≥ Grade 3 rash or photosensitivity lasting > 7 days despite optimal treatment
Fatigue	Grade 3 fatigue lasting > 7 days
Immune related toxicities (except pneumonitis)	Grade 3 immune related toxicities lasting > 7 days despite optimal treatment
Others	Any other ≥ Grade 2 toxicity that in the opinion of the investigator and agreed with the Medical Monitor is considered to be a clinically unacceptable risk

For any TLT event occurring during the first 4 weeks of treatment, study treatment will be discontinued permanently. For any TLT event occurring after successful completion of 4 weeks

of treatment, provision is made for dose modification (see Section 6.1.7). If excessive TLTs are observed anytime during the trial, a dose de-escalation can be enforced following DRC review or the trial can be stopped at the sponsor's discretion (see Section 8.6.2).

5.7. Definitions and Procedures Related to Disease Progression

Patients will be assessed for clinical and/or radiological progression throughout the study using the screening assessments as the baseline for determination of changes.

- Patients will have clinical disease assessments (e.g., ECOG performance status and evaluation of AEs, including new signs or symptoms of disease) throughout the study.
  - Patients who demonstrate clinical deterioration should be discontinued from study treatment.
- Patients will have radiological disease assessments at study entry and every 8 weeks for the first 12 months while on treatment and every 12 weeks thereafter; unscheduled assessments may be conducted in response to new clinical observations. Disease status will be classified according to RECIST v1.1 [Eisenhauer 2009] (see Section 7.1.4.2 for details).
  - For patients with radiological evidence of PD compared to study baseline, study treatment may be discontinued; however, patients may remain on study if the Investigator determines that continued treatment with the combination of nivolumab and X4P-001 is in the patient's best interests (see requirements in Section 5.7.1).

5.7.1. Continuation of Treatment Beyond Radiologic Disease Progression

Recent publications suggest that some patients treated with immunotherapy may benefit from continued treatment despite meeting the radiological criteria for PD [Wolchok 2009]. In consideration of these observations, patients enrolled in the study who meet radiological criteria for PD will be allowed to continue receiving study treatment if they meet *all* of the following criteria:

- In the judgment of their Investigator, *all* of the following apply:
  - The patient is not demonstrating clinically significant symptoms of PD.
  - The patient is tolerating study treatment.
  - The patient has experienced, or has the potential to experience, clinical benefit from continuing to receive study treatment.
- Both the Investigator's recommendation to continue treatment and the concurrence of the Medical Monitor are documented in the study records.

Patients who continue treatment under this provision will have ongoing, regularly scheduled clinical and radiologic assessments as per protocol. Study treatment should be discontinued if patients meet *either* of the following criteria:

- Clinical evidence of PD.
- Further radiological progression, defined as an immune confirmed progressive disease (iCPD) based on iRECIST criteria [Seymour 2017]. Below is an overview of iRECIST assessment of progressive disease; reference Seymour et al. for more details.
  - Immune unconfirmed progressive disease (iUPD) is defined by RECIST 1.1 criteria for progressive disease.
  - For target lesions, progression is confirmed if the next imaging assessment after iUPD (4–8 weeks later) confirms a further increase in sum of measures of target disease from iUPD, with an increase of at least 5mm.
    - However, the criteria for iCPD (after iUPD) are not considered to have been met if complete response, partial response, or stable disease criteria (compared with baseline and as defined by RECIST 1.1) are met at the next assessment after iUPD.
  - For non-target lesions, progressive disease is confirmed if subsequent imaging done 4–8 weeks after iUPD, shows a further increase from iUPD.
    - The criteria for iCPD are not judged to have been met if RECIST 1.1 criteria for complete response or non-iCR/non-iUPD are met after a previous iUPD.
  - For new lesions, progressive disease is confirmed (iCPD) if the next imaging assessment, done at 4–8 weeks after iUPD, confirms additional new lesions or a further increase in new lesion size from iUPD (≥5 mm increase in sum of measures for new target lesion, or any increase for new non-target lesion).

6. STUDY DRUG(S)

6.1. Study Drug(s) and Control Description

The investigational agent is X4P-001, which will be administered in combination with nivolumab (OPDIVO®), a PD-1 blocking antibody approved for the treatment of patients with advanced RCC who have received prior anti-angiogenic therapy.

6.1.1. Acquisition

X4P-001 will be supplied by the Sponsor. Nivolumab will be supplied by prescription from commercial supplies.

6.1.2. Formulation, Appearance, Packaging, and Labeling

All manufacture, packaging and labeling operations will be performed according to Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) guidelines, as well as US regulations.

6.1.2.1. X4P-001

Table 6-1: Physical and Chemical Properties of X4P-001 Active Ingredient (Drug Substance)

Name	X4P-001
Drug Class	Chemokine (C-X-C motif) receptor 4 (CXCR4) antagonist
INN	Not Assigned
Molecular Formula	$C_{21}H_{27}N_5$
Molecular Weight	349.48 amu
Appearance	white to pale yellow solid
Solubility	X4P-001 is freely soluble in the pH range 3.0 to 8.0 (>100 mg/mL), sparingly soluble at pH 9.0 (10.7 mg/mL) and slightly soluble at pH 10.0 (2.0 mg/mL). X4P-001 is only slightly soluble in water.
Melting Point	111.4°C

Table 6-2: Formulation of X4P-001 Drug Product

Name	X4P-001 100 mg or 200 mg Capsule
Active ingredient	X4P-001
Excipients	Dibasic calcium phosphate dihydrate, microcrystalline cellulose, croscarmellose sodium, sodium stearyl fumarate, colloidal silicon dioxide, sodium lauryl sulfate
How supplied	Dispensing instructions will be provided in the Pharmacy Manual
Storage	5°C ± 3°C; Protect from light and humidity
Administration	Oral

6.1.2.2. Nivolumab

Please refer to the package insert for a description of nivolumab.

6.1.3. Product Storage and Stability

6.1.3.1. X4P-001

See Table 6-2.

6.1.3.2. Nivolumab

Please refer to the package insert for nivolumab storage conditions.

6.1.4. Preparation

6.1.4.1. X4P-001

None.

6.1.4.2. Nivolumab

Nivolumab will be prepared and administered in the clinic according to the current package insert and institutional guidelines.

6.1.5. Dosing and Administration

6.1.5.1. X4P-001

X4P-001 400 mg is administered PO QD as follows:

- The daily dose should be taken in the morning, at the same time each day ± 2 hr.
- The interval between successive doses should not be <20 hrs.
- If the interval between successive doses is delayed to >30 hrs, the dose should be omitted and the usual schedule resumed the next day.
- There should be no food or drink (except water) for 1 hour prior to dosing and continuing until 2 hours post-dose.

Patients for whom the scheduling requirements and eating restrictions represent significant difficulties should be discussed with the Medical Monitor to develop the most effective regimen possible.

6.1.5.2. Nivolumab

Investigators should review and be familiar with the current prescribing information for nivolumab (February 2017).

All patients will have received nivolumab as per standard of care prior to enrollment to the study. Enrolled patients will continue treatment with nivolumab at 240 mg every 2 weeks by

intravenous (IV) infusion over 60 minutes using a sterile, non-pyrogenic, low protein binding in-line filter with pore size of 0.2 to 1.2 micrometer. Other drugs should not be administered concurrently through the same IV line.

6.1.6. Route of Administration

6.1.6.1. X4P-001

X4P-001 will be administered PO.

6.1.6.2. Nivolumab

Nivolumab will be administered IV.

6.1.7. Dose Adjustments/Modifications/Delays

The procedures detailed below should be used to guide treatment modifications in response to AEs, including TLTs and/or immune-mediated events. The specific criteria and procedures reflect the current nivolumab label, the available clinical and nonclinical experience with X4P-001, and the recognition that both components of the study treatment regimen modulate the immune system. Treatment modifications should be implemented as described. Investigators and patients always have the option to discontinue study treatment based on their judgment of the patient's best interests.

Note that the Schedules of Events (Table 1-1), including the 28-day cycles, are based on calendar days following the first dose (defined as Day 1). These schedules will not change, that is, a dose of nivolumab or X4P-001 that is held will be considered to have been skipped; dose delays are not permitted.

For dose modifications due to concomitant use of strong inhibitors and inducers of CYP3A4, see Section 7.4.1.1.

Table 6-3 displays the treatment modification guidelines in response to specific adverse reactions (AEs that are considered as treatment-related). These guidelines apply to both study treatments, X4P-001 and nivolumab. In the event of AEs, study treatment may, *with the agreement of the patient, the Investigator, and the Medical Monitor*, be managed as follows:

- If the event does *not* improve to Grade ≤1 within the next 6 weeks, study treatment will be permanently discontinued.
- If the event improves to Grade ≤1 within 6 weeks of holding study treatment, the patient may resume nivolumab and X4P-001. X4P-001 can be resumed immediately. Nivolumab dose will be resumed at the next scheduled time. Note that consistent with current label recommendations, nivolumab dose reductions are not permitted. For AEs ≤ Grade 2, X4P-001 can be given at the same dose (400 mg QD). For AEs ≥ Grade 3, X4P-001 will be resumed at a lower dose (200 mg QD).

- If the event recurs to the same severity or greater *at any time* after resuming the study drugs, study treatment will be discontinued.

Concomitant management of immune-mediated reactions, as defined in the nivolumab label:

- If immune-mediated reactions occur, the Investigator may administer corticosteroids at 0.5 to 2 mg/kg/day prednisone equivalent, depending on the nature and severity of the event. For endocrine-related events initiate hormone-replacement therapy, if appropriate.
  - Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month.

Table 6-3: Recommended Treatment Modifications for Nivolumab and X4P-001

Adverse Reaction	Severity	Treatment Regimen Modification[1]
Colitis	Grade 2 or 3 diarrhea or colitis	Withhold dose[2]
	Grade 4 diarrhea or colitis	Permanently discontinue
Pneumonitis	Grade 2 pneumonitis	Withhold dose[2]
	Grade 3 or 4 pneumonitis	Permanently discontinue
Hepatitis	AST or ALT >3x up to 5x ULN *or* total bilirubin >1.5x up to 3x ULN	Withhold dose[2]
	AST or ALT >5x ULN *or* total bilirubin >3x ULN	Permanently discontinue
Hypophysitis	Grade 2 or 3 hypophysitis	Withhold dose[2]
	Grade 4 hypophysitis	Permanently discontinue
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Withhold dose[2]
	Grade 3 or 4 adrenal insufficiency	Permanently discontinue
Type I Diabetes Mellitus	Grade 3 hyperglycemia	Withhold dose[2]
	Grade 4 hyperglycemia	Permanently discontinue
Nephritis / Renal Dysfunction	Serum creatinine >1.5x up to 6x ULN	Withhold dose[2]
	Serum creatinine >6x ULN	Permanently discontinue
Skin	Grade 3 rash or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold dose[2]
	Grade 4 rash or confirmed SJS or TEN	Permanently discontinue
Encephalitis	New onset moderate or severe neurologic signs or symptoms	Withhold dose[2]
	Immune-mediated encephalitis	Permanently discontinue

Adverse Reaction	Severity	Treatment Regimen Modification[1]
Infusion Reaction	Grade 1 and 2	Interrupt or slow the rate of nivolumab infusion. Provide proper medication and symptomatic relief as needed. No dose modification for X4P-001.
	Grade 3 and 4	Discontinue nivolumab infusion immediately. Provide proper medication and symptomatic relief. No dose modification for X4P-001.
Retinal Abnormality	Grade 1	Monitor closely (No dose modifications).
	Grade 2	Withhold dose of X4P-001. No dose modification for nivolumab.
	Grade 3 and 4	Permanently discontinue X4P-001. No dose modification for nivolumab.
Other Events	Other Grade 3 AE First Occurrence Recurrence of same Grade 3 AE	 Withhold dose[2] Permanently discontinue
	Any Grade 4 (life-threatening) AE	Permanently discontinue
	Any event that requires treatment for >12 weeks with prednisone ≥10 mg/day (or equivalent)	Permanently discontinue
	Any Grade 2 or 3 AEs persisting ≥12 weeks	Permanently discontinue

1. Regimen modifications apply to *both* nivolumab and X4P-001 unless otherwise specified.
2. See text for details of procedures for resuming study treatment.

6.1.8. Duration of Therapy

Patients are expected to receive study treatment until the earliest of:

- *TLT event* – see Section 5.6.
  - For any TLT event occurring within Cycle 1, study treatment will be discontinued permanently.
  - For TLT events occurring after Cycle 1, provision is made for dose interruption (see Section 6.1.7).
- PD – see Section 5.7.

6.1.9. Treatment Compliance

Treatment compliance with X4P-001 will be monitored by 2 procedures.

- Patients will be provided with treatment diary to record time and dose level taken for both X4P-001, as well as time of last food prior to and after dosing X4P-001. Diaries will be reviewed with the patient at each clinic visit.
- X4P-001 will be dispensed in bottles, which will be examined visually at each clinic visit; non-destructive pill counts will be performed if indicated.

6.2. Study Drug Accountability Procedures

The US FDA and other applicable regulatory authorities require accounting of all investigational drug received by each study center. Records of drug disposition required include the date received by the center, date administered, quantity administered, and the patient to whom study drug was administered. The Investigator is responsible for the accountability of all used and unused study drug containers and unused study drug. For the Combination Cohort(s), the study center also will maintain records for the combination anticancer agent, including the date administered, quantity administered, and the patient to whom the agent was administered.

Each study center is to use a study drug accountability log to document study drug disposition. All items on this form are to be completed in full. The Sponsor's clinical research associate (CRA) is to approve the area where study drug is to be stored and accountability records are to be maintained.

The investigator identification number and patient initials (as allowed by local regulations) and identification number are to be recorded on each study drug accountability log. Each time study personnel dispense study drug for a patient, he or she is to record the date dispensed, amount of study drug dispensed, and his or her initials. Study personnel are to monitor the inventory of clinical supplies and maintain a count of all used and unused study drug. The CRA is to review study drug accountability records and remaining drug supplies during routine monitoring visits.

At the completion of the study, the site must obtain written authorization from the Sponsor regarding the final disposition of any remaining X4P-001; that disposition must be appropriately documented. Typical procedures for handling any remaining study drug include the following:

- Returning study drug to the Sponsor.
- Destroying study drug at the study site according to the site's institutional standard operating procedure.

7. STUDY PROCEDURES AND SCHEDULE

7.1. Study Procedures/Evaluations

Table 1-1 details the schedules for all study evaluations.

The schedule is presented relative to cycle, day within cycle, and time of dosing. Each cycle represents 4 weeks (28 days). The calendar day of the first administration of X4P-001 is designated Cycle 1, Day 1. Pre- and post-dose intervals are relative to the time of oral administration of X4P-001, designated 0 hr.

7.1.1. Baseline and Safety Assessments

Written informed consent will be obtained and the consent procedure recorded in source documentation before any other study-specific procedures are performed.

7.1.1.1. Enrollment Procedure

Enrollment in this protocol will be open across all activated sites. At the discretion of the Sponsor, a site that enrolls ≥6 (30%) of the anticipated 20 patients may be capped.

The following procedure is implemented to assure that eligibility of all patients is reviewed and approved by the Sponsor (or representative, e.g., Medical Monitor). Site personnel will access an interactive voice- or web-based enrollment system, confirm eligibility, and indicate that the patient is being proposed for enrollment (for details, including requirements for eCRF data entry, reference the study operational manual). In the event of any discrepancies or other issues, the request will be referred to the Medical Monitor or designated study personnel for review.

After acceptance, the Investigator and site pharmacy will be provided written confirmation (by email and/or fax) of the patient's acceptance for enrollment. Enrollment will be defined as completing baseline evaluation and receiving at least one dose of X4P-001.

7.1.1.2. Demographics and Medical History

General Medical History

A complete medical history is to be documented during Screening, including relevant general medical and surgical history, current or past abnormalities or diseases of the following systems: allergic (including drug sensitivity), cardiovascular, dermatologic, endocrine/metabolic, gastrointestinal, gynecologic, hematologic/lymphatic, hepatic/biliary, immunologic, infectious, musculoskeletal, neurologic/psychiatric, renal, and respiratory.

The medical history should include all significant illnesses and hospitalizations that occurred in the past 6 months, whether active or resolved. Illnesses active at the time of informed consent will be recorded in the medical history.

History of Renal Cell Carcinoma (RCC)

Detailed history of the course of the patient's RCC will be recorded, including:

- Prior surgical procedures, diagnostic or therapeutic.
- Results (positive and negative) of prior tissue biopsies.
- Prior medical treatments (including supportive therapy) – agent, duration, best clinical response, adverse events related to treatment, and reason for discontinuation.
- Hospitalizations for clinically significant complications of the treatments or the malignancy, e.g., systemic infections, bleeding.
- Historical tumor measurements from prior to starting nivolumab through the screening period.

7.1.1.3. Vital Signs

Vital signs include heart rate (HR), blood pressure (BP), and temperature. Where feasible, vital signs should be measured before blood is drawn and after the patient has been sitting comfortably for 5 minutes with the BP cuff in place on the non-dominant arm. BP and HR measurements will be taken first and may be done manually or by automated recorder. Temperature will be obtained using an electronic (rapid reading) device.

Vital sign measurements will be assessed by the Investigator as either 'normal', 'abnormal, not clinically significant', or 'abnormal, clinically significant'. Clinically significant abnormal vital sign measurements will be reported as an AE, and, if possible, should be repeated at clinically relevant intervals until resolved or stabilized.

7.1.1.4. Physical Examination and Body Weight

Complete physical examinations will include measurement of body weight and examination of general appearance, skin, neck (including thyroid), eyes, nose, throat, heart, lungs, abdomen, lymph nodes, extremities, and nervous system. Body height will be measured at screening only.

- For palpable lymph nodes, the location and maximal linear dimension will be recorded at each examination.
- Examination of the reproductive system will be performed if there are related symptoms, adverse events, or recent history; the exam may be performed by the Investigator or delegated to a specialist.

Physical examination findings will be assessed by the Investigator as either 'normal', 'abnormal, not clinically significant', or 'abnormal, clinically significant'. Any clinically significant changes identified after the baseline (screening) examination will be recorded as AEs (see Section 8).

7.1.1.5. Ophthalmologic Examination

Ophthalmologic examinations will be performed as scheduled and include the following elements: assessment of visual acuity (using Snellen test), refraction (at screening only), assessment of color vision, slit lamp examination, and retinal examination with photographs. Please refer to the study operational manual for details. All examination reports and photographs will be submitted to a central repository as soon as feasible after being performed to be reviewed for quality and completeness (see study operational manual for details).

Retinal abnormalities noted at screening will be discussed with the Medical Monitor. Examination by a second ophthalmologist may be requested to confirm the description of the findings and the adequacy of the photographs. Enrollment may proceed with the approval of the Medical Monitor.

Any patient reported to have treatment-emergent findings of retinopathy will be examined by a second ophthalmologist.

All examination reports and photographs may be reviewed by an independent, blinded ophthalmologist designated by the Sponsor.

7.1.1.6. ECOG Performance Status (PS)

The ECOG PS will be obtained by questioning the patient about their functional capabilities, according to Table 7-1.

Table 7-1: ECOG PS Definitions

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

7.1.1.7. Electrocardiogram

Standard 12-lead ECG will be obtained after the patient has been semi-recumbent for ~10 minutes. The following ECG parameters will be recorded: ventricular rate, RR interval, PR interval, QRS interval, QT interval, QTc interval, and QTc method.

7.1.2. Pharmacokinetic Assessments

PK samples will be obtained on all patients as follows:

- Cycle 1, Day 1: pre-dose only (-30 min)
- Cycle 1, Day 8: pre-dose only (-10 min)
- Cycle 1, Day 15: pre-dose only (-10 min)
- Cycle 1, Day 22: pre-dose (-10 min); post-dose at 60, 90 min (each ±10 min) and 2, 3, 4, 8 hr (each ±15 min)
- Cycle 3, Day 1: pre-dose only (-10 min)

These visits will be scheduled for early in the day and patients will be instructed to arrive at the clinic fasting and having not taken their dose of X4P-001.

If results suggest either (a) ongoing accumulation or (b) specific exposures associated with adverse effects, then additional PK samples may be collected.

Samples will be analyzed for X4P-001 concentration using reversed-phase high performance liquid chromatography with tandem mass spectrometry detection.

7.1.3. Pharmacodynamic Assessments

Investigational assays will be performed by a central laboratory designated by the Sponsor; to maximize consistency, tests may be batched. The clinical significance of these tests is unknown at this time, and the results will not be assessed by the Investigator.

7.1.3.1. Blood Samples

Whole blood samples for pharmacodynamic analysis will be obtained concurrently with scheduled PK samples on Cycle 1 Day 22 only (see Section 7.1.2) and sent to the local laboratory for WBC counts, including ANC and ALC.

In addition, PBMC and serum samples will be collected as scheduled and assayed by a central laboratory for potential treatment- and tumor-related biomarkers (Table 7-2).

Table 7-2: Candidate Blood Biomarkers

Serum	PBMC [Tarhini 2014]
CXCL12 VEGF	Treg lymphocytes Activated T cells MDSCs

7.1.3.2. Tissue Biomarkers

If available, unstained slides prepared from formalin fixed paraffin embedded (FFPE) tumor samples from the patient's most recent tumor sampling will be collected and analyzed for biomarkers that are potentially associated with sensitivity and resistance to combination treatment with X4P-001 and nivolumab. Candidate markers include CXCR4, CXCL12, CD3, CD8, and myeloid markers; additional or alternative biomarkers may be explored using the samples obtained for biomarker analysis.

Approximately 125µm of tumor sample is required for this purpose. Directions for processing the archived FFPE blocks are included in the study laboratory manual; briefly, 15 (5 micron slides) and 5 (10 micron slides) are requested.

7.1.4. Efficacy Assessments

7.1.4.1. Radiologic Assessment of ccRCC

Radiologic imaging of chest, abdomen and pelvis for assessing tumor status and treatment effect will be performed as indicated in the Schedules of Events. Interim assessments may be done at the request of the Investigator based on new findings. Patients enrolled with a history or current evidence of CNS disease will have brain imaging by magnetic resonance imaging (MRI) with contrast at baseline and, thereafter, as clinically indicated.

Imaging will be interpreted using RECIST v1.1 [Eisenhauer 2009] (see Section 7.1.4.2). The expected imaging technology is CT with slice thickness ≤5 mm and contrast. The use of alternative technologies (e.g., CT scan with slice thickness >5 mm or MRI) requires the approval of the Medical Monitor and must be performed in a manner consistent with RECIST. For each patient, the imaging modality should be consistent throughout the study. If there is a need to change modality (e.g., a patient cannot receive radiologic contrast), an alternative modality may be used with the approval of the Medical Monitor.

For clinical management during the study, imaging will be interpreted by the radiologist at the site; however, patients who, in the judgment of the Investigator, have derived clinical benefit may continue to receive study treatment until clinical deterioration (see Section 5.7.1).

7.1.4.2. Evaluation of Response to Treatment and Disease Status

Tumor Response. Radiologic assessments will be conducted every eight (8) weeks (every other cycle) during the first 12 months; every 12 weeks (every third cycle) thereafter; at EOT (if not performed in the prior 4 weeks); or as indicated based on new signs, symptoms or laboratory findings. Disease status, time to progression, duration of response, and PFS will be determined based on RECIST v1.1 [Eisenhauer 2009]. Treatment decisions will be made by the Investigator incorporating the local radiology interpretation and, if necessary, consultation with the Medical Monitor (see Section 5.7.1). Patients enrolled with a history or current evidence of CNS disease will have brain imaging by MRI with contrast at baseline and, thereafter, as clinically indicated.

In addition to the radiologic assessments collected while on study, an effort will be made to collect imaging studies and/or tumor measurements over the period from the start of treatment with nivolumab until enrollment in this study.

The current (v1.1) RECIST provide a detailed process for using sequential CT imaging to classify tumor response [Eisenhauer 2009]. Key elements of the process are summarized below; details provided in the guideline remain determinative. NOTE: all specifications assume use of CT with slice thickness ≤5 mm. Modifications are required for other technologies.

Definitions of key terminology:

- Measurable non-nodal lesions – ≥10 mm in longest diameter.
- Measurable nodal lesions – ≥15 mm in short axis
- Nonmeasurable lesions – lesions that are smaller, including those that cannot be measured.
- Measurable disease – presence of at least one measurable lesion. [NOTE: Entry into this study requires at least one measurable extra-renal lesion.]
- Target lesions – At baseline, a maximum of 5 measureable lesions, no more than 2 for any individual organ, should be identified, documented, and the appropriate diameter of each recorded. Lesions should be selected based on size, be representative of disease, and be suitable for reproducible repeat measurement. Target lesions may include measurable lymph nodes.
- The baseline sum of diameters (SOD) – The sum of the longest diameters for all non-nodal target lesions plus the sum of the short axis diameter for all nodal target lesions.
- Non-target lesions – All other lesions present at baseline, including pathologic nodes (defined as nodes >10 mm in short axis). These should be documented (quantitative measurements are not required) so that they can be classified on follow-up as present, absent, or unequivocal progression.
- New lesions – a new lesion should be unequivocal (e.g., not attributable to variation in technique); includes lesions in a location *not* scanned at baseline.
- Definitions of response criteria for target and non-target lesions are summarized in Table 7-3; these are integrated into an overall response assessment as summarized in Table 7-4.

Table 7-3: RECIST – Definitions of Response Categories for Target and Non-Target Lesions

Target Lesions	
Complete Response (CR)	(a) Disappearance of all non-nodal lesions, *and* (b) Absence of pathologic lymph nodes[1].
Partial Response (PR)	≥30% decrease from baseline in the SOD of the target lesions
Stable Disease (SD)	Persisting disease that does not meet criteria for either PR or PD
Progressive Disease (PD)	a) ≥20% increase in the SOD of the target lesions, compared to the smallest sum on study, which may be either at baseline *or* while on treatment; *and* (b) an absolute increase of ≥5 mm in the SOD.
Non-Target Lesions	
Complete Response (CR)	(a) Disappearance of all non-target lesions, *and* (b) Absence of pathologic lymph nodes[1].
Non-CR/non-PD	Persistence of one or more non-target lesions
Progressive Disease (PD)	*Unequivocal progression* of existing non-target lesions.

1. All lymph nodes, whether or not designated target or non-target lesions, have short axis diameter ≤10 mm

Table 7-4: RECIST – Overall Responses Based on Target Lesions, Nontarget Lesions, and New Lesions

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	
PR	Non-PD or not all evaluated	No	
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Non-evaluable
CR, PR, or SD	PD[1]	No	PD
PD	Any	Yes or no	
Any	Any	Yes	

1. "The designation of overall progression *solely* on the basis of change in non-target disease" in the face of CR, PR, or SD of target lesions is expected to be "extremely rare" [Eisenhauer 2009].

7.1.4.3. Exploratory Analysis of Efficacy Using iRECIST

Tumor response assessments may be explored by using the iRECIST [Seymour 2017]. Details of this assessment will be defined in statistical analysis plan (SAP) and/or study operational manual.

7.2. Laboratory Procedures/Evaluations

7.2.1. Clinical Laboratory Evaluations

The laboratory safety tests listed in Table 7-5 will be performed as scheduled by a central laboratory facility. The Investigator may order additional local laboratory tests consistent with their routine standard of care.

Table 7-5: Safety Laboratory Tests

Hematology Panel	
Hematocrit	WBC differential and absolute cell counts:
Hemoglobin	Basophils
Platelet count	Eosinophils
WBC count	Lymphocytes
	Monocytes
	Neutrophils
Clinical Chemistry Panel	
ALT	Glucose
Albumin	Inorganic phosphorus
Alkaline phosphatase	Lipase
Amylase	Magnesium
AST	Potassium
Bicarbonate	Sodium
Calcium	TBIL**
Chloride	Total protein
Creatine kinase (CK)	Urea
Creatinine*	Uric acid
*Creatinine clearance will be calculated using the method of Cockcroft and Gault (Cockroft, Gault, 1976).	
** If the total bilirubin concentration is above 1.5 times the upper limit of normal, direct and indirect bilirubin should be differentiated.	
Coagulation Panel	
Activated partial thromboplastin time	International normalized ratio
Urinalysis	
Blood (commercial dipstick may be used)	pH
Glucose	Protein
Ketones	Specific gravity
Microscopic examination, including quantitation of WBCs, red blood cells, and casts	
Thyroid Function Tests (Parts A and B only)	
Free thyroxin	Thyroid stimulating hormone

Pregnancy tests (WOCP only)	
beta-human chorionic gonadotropin	
Serologic tests (Screening only)	
HBsAg	Antibody to HCV

7.2.1.1. Reporting of Safety Laboratory Tests

Results of safety laboratory tests (except serology) are expected to be available to the Investigator within 48 hours. Procedures for the Investigator assessment of the results are detailed in Section 8.1.5. Procedures for the analysis of laboratory data are described in Section 8.2.2.

7.2.1.2. Repeating Abnormal Laboratory Tests

Laboratory tests showing abnormal or exclusionary values at Screening may be repeated no more than once; however, exclusionary serologic results may not be repeated.

After dosing, abnormal laboratory tests assessed as "clinically significant" values may be repeated as often as deemed clinically necessary by the Investigator until the test values are clinically acceptable or until an explanation other than drug effect is given.

7.2.2. Other Assays or Procedures

None.

7.2.3. Specimen Preparation, Handling, and Storage

Laboratory samples are to be prepared, handled, and stored as instructed in the laboratory manual.

7.2.4. Specimen Shipment

Laboratory samples are to be shipped as instructed in the laboratory manual.

7.3. Study Schedule

The schedule of events is presented in Table 1-1.

- Note: in all contexts, "days" refers to calendar days.
- Screening will be done within 28 days prior to Day 1 (the first dose of study drug). See Table 1-1 for details of screening and Section 7.1.1.1 for details of the enrollment process.
- Assessments for treatment response (or PD) are scheduled every 8 weeks (±4 calendar days) during the first 12 months of treatment and every 12 weeks (±4 calendar days) thereafter (see Sections 5.7 and 7.1.4).

- EOT visit will be performed within 6 days after the last dose of study drug or the decision to terminate treatment prematurely.
- EOS visit, the final study event, will be performed 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.
- Extension Phase: Provision is made for the Sponsor to analyze the study data after all enrolled patients have completed at least 12 months of treatment. Patients receiving study treatment at that time may continue to receive treatment during an extension phase of the protocol, with an adjusted schedule of assessments and limited central data collection (see Section 7.3.1 for details).

7.3.1. Extension Phase

Provision is made for performing the final analysis for the study provided all of the following criteria are met:

- Enrollment has been closed.
- All ongoing patients have completed at least 12 months of study treatment.
- All ongoing patients are clinically stable (or improved) at their last evaluation.

If the Sponsor elects to analyze the study data prior to the discontinuation of all patients, ongoing patients will enter the extension phase of the study and may continue to receive study drug until PD or unacceptable toxicity, whichever occurs first (see Section 5.4.1 for treatment termination criteria). The patient's participation in the extension phase will be complete when study treatment is discontinued.

The following procedures will apply during the extension phase:

- Full safety reporting requirements as detailed in Section 8.4 will apply to the following events:
  - All SAEs, as defined in Section 8.1.2.
  - Any AE which in the Investigator's judgement occurred at greater incidence or severity than presented in the Investigator Brochure.
- Follow-up for safety and disease evaluation will be conducted as per routine standard of care.
- Collection of other data will be limited to radiologic imaging and AEs.

7.4. Concomitant Medications, Treatments, and Procedures

Any concomitant medication used from time of screening through last study visit will be recorded in the eCRF, including dose, regimen, and indication (reason for its prescription).

7.4.1. Precautionary Medications, Treatments, and Procedures

7.4.1.1. Restrictions related to CYP Interactions

X4P-001 is metabolized through, and interacts with, the CYP metabolic enzymes found in the hepatic and intestinal microsomes (see Section 2.2.2.3 for details). Based on these observations, the following restrictions are placed on concomitant medications:

- Strong inhibitors and inducers of CYP3A4 are prohibited. If a strong inhibitor or inducer cannot be avoided, the dose of X4P-001 can be reduced with approval of Medical Monitor.
- Grapefruit and/or starfruit products, variable inhibitors of CYP3A4, are prohibited.
- Moderate inhibitors and inducers of CYP3A4 are to be prescribed only with the approval of the Medical Monitor; additional monitoring of X4P-001 drug levels may be required.
- Sensitive CYP2D6 substrates should be avoided and other CYP2D6 substrates should be administered only with the approval of the Medical Monitor.

Appendix Section 18.2 provides a list of commonly prescribed drugs that are inhibitors or inducers of CYP3A4 and substrates of CYP2D6. Known strong inducers and inhibitors are indicated. This list of drugs may not be a complete list, consultation with the medical monitor is requested for any concerns about concomitant medication use.

7.4.1.2. Non-childbearing Potential

Non-childbearing potential is defined as a female who meets ***either*** of the following criteria:

- Age ≥50 years and no menses for at least 1 year.
- Documented hysterectomy, bilateral tubal ligation, or bilateral oophorectomy.

7.4.1.3. Effective Birth Control (Contraception) Methods

Women of childbearing potential (WOCP) must use a highly effective method of contraception during the study, and through 5 months after the last dose of nivolumab or through 4 weeks after the last dose of X4P-001, whichever is latest. Acceptable methods include:

- hormonal contraceptives when used with an additional barrier method (e.g., a male condom):
  - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - oral
    - intravaginal
    - transdermal

  - progestogen-only hormonal contraception associated with inhibition of ovulation:
    - oral
    - injectable
    - implantable
- intrauterine device (IUD).
- intrauterine hormone-releasing system (IUS).
- bilateral tubal occlusion.
- vasectomized partner who has received a medical assessment of surgical success (when the partner is the sole partner).
- sexual abstinence (when in agreement with the lifestyle and preference of the WOCP).

Fertile males are required to use a male condom with any WOCP sexual partner during the study, and through 5 months after the last dose of nivolumab or through 4 weeks after the last dose of X4P-001, whichever is latest.

7.4.2. Prohibited Medications, Treatments, and Procedures

The exclusion criteria specify treatments prohibited at the time of study entry (Section 5.2).

While patients are receiving study treatment, other treatments for ccRCC are prohibited. Patients who discontinue treatment prematurely and have completed the EOT visit, may receive available or investigational treatment for their disease at any time based on the judgment of their physician. If such treatment is initiated prior to the EOS visit, this will be recorded in concomitant medications and considered in assessment of any new AE.

7.4.3. Prophylactic Medications, Treatments, and Procedures

None.

7.4.4. Rescue Medications, Treatments, and Procedures

7.4.4.1. Treatment of Expected Adverse Events

Based on prior clinical experience (as detailed in Section 2.2.1), the following treatments are recommended for symptomatic relief of "red eye", "dry eye", nasal congestion (in some instances with nosebleed), facial pains, and diarrhea which may occur within 48 hours of initiation of treatment:

- Lubricant eye drops containing carboxymethylcellulose sodium (0.5%), such as Refresh™ Tears
- Non-medicated saline nasal spray, such as Simply Saline™ Nasal Mist (Arm & Hammer)

- Acetaminophen (Tylenol™)
- Diarrhea should be managed according to institutional standard of care.

7.4.5. Precautions Regarding Nivolumab

Please refer to nivolumab prescribing information for all warnings and precautions related to this drug.

7.4.6. Patient Restrictions during the Conduct of the Study

In the interest of their safety and to facilitate assessment of both safety and treatment effect, the patients participating in this study will be requested to agree to the following restrictions during the study:

- Not start any new prescription medications, except as prescribed or approved by their Investigator or if required in an emergency;
- Not take any over-the-counter medications, except as instructed or approved by their Investigator.
- Not drink grapefruit juice or eat grapefruit/starfruit.
- Use effective contraception as defined in Section 7.4.1.3.

7.5. Appropriateness of Measurements

Planned assessments are standard measurements for this type of study and are considered appropriate. Per regulatory guidance, demographic data, complete medical histories, including cancer treatment history, and Baseline disease status are to be documented for all patients at Baseline [FDA Guidance for Industry 2001].

AEs and SAEs are monitored in this study in accordance with International Conference on Harmonisation (ICH) GCP guidelines to ensure the safety of patients. Furthermore, additional safety assessments conducted during this study, including physical examinations, ECGs, vital signs assessments, and clinical laboratory tests, are widely used and generally recognized as reliable, accurate, and relevant. These tests and procedures also will be monitored in accordance with ICH GCP guidelines.

Tumor response and progression will be assessed using standard criteria for the assessment of disease response in solid tumors, RECIST, v1.1.

8. ADVERSE EVENTS

8.1. Definitions

8.1.1. Adverse Events (AE)

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

An AE in a clinical study may be any of the following:

- An unfavorable and unintended symptom reported by the patient. Patients will be encouraged to report treatment-emergent AEs spontaneously; general, non-directed questioning may also be used to elicit reports of AEs.
- Clinical sign detected by the Investigator. Observations by other study personnel will be reported to the Investigator for evaluation.
- Abnormal result from a laboratory study or other diagnostic procedure that meets at least one of the following criteria:
  - Results in termination of study drug;
  - Leads to treatment;
  - Leads to further diagnostic tests (other than a single repeat for confirmation);
  - Is assessed as "clinically significant" by the Investigator.

8.1.2. Serious Adverse Events (SAE)

An AE or suspected adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it:

- Results in death.
- Is life-threatening. Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.

- Requires in-patient hospitalization or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected manner during the study (e.g., surgery performed earlier than planned). Additional exclusions to SAE reporting include hospitalizations for:
  - Elective procedures.
  - Social/administrative reasons in the absence of an AE.
  - Expected deterioration caused by progression of the disease under study.
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.
- Is an important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

8.1.3. Adverse Drug Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "responses to a medicinal products" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

8.1.4. Suspected, Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is defined as an SAE that meets both the following criteria with respect to study drug:

- Suspected — is assessed as related or possibly related to study drug (see Section 8.2.2);
- Unexpected — compared to the study drug-related AEs described in Investigator's Brochure, the event meets any of the following criteria:
  - The event was not previously described;
  - The event is now characterized as more severe (see Section 8.2.1);

- The event is now characterized more specifically (e.g., an event of "interstitial nephritis" in a patient receiving an agent previously described as associated with "acute renal failure").

In clinical studies involving ill patients, events considered related to the natural history of the disease under study or to lack of efficacy (that is, the event is considered more likely related to those factors than to other factors, including study drug) are not considered "unexpected".

8.1.5. Clinical Laboratory Adverse Events

The Investigator will review the results of all Safety Laboratory tests (see Section 7.2.1) and designate any results outside of the reference range as ***either*** of the following:

- Abnormal, not clinically significant (NCS)
- Abnormal, clinically significant (CS).

In making this judgment, the Investigator will consider all available information, including the patient's clinical condition, all available laboratory results, and the potential for false positive test results. In addition, laboratory studies that result in the actions specified in Section 8.1.1 will be classified as "abnormal, clinically significant".

Any result assessed as "abnormal, clinically significant" will be recorded as an AE *unless* it is consistent with one or more of the following:

- Process noted in the medical history:
- Ongoing adverse event already recorded;
- Expected course of the primary disease under study.

8.2. Classification of Adverse Events

8.2.1. Severity

The intensity (synonym: severity) of clinical AEs (i.e., symptoms reported by the patient and/or signs observed by the Investigator) will be assessed by the Investigator using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) (v4.03) five-level grading system, available on-line (see http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf).

If the AE is not included in the NCI CTCAE, then the Investigator is to determine the intensity of the AE according to the following criteria:

- ***Mild (Grade 1):*** AE that disappears or is easily tolerated on continuation of study drug.
- ***Moderate (Grade 2)***: AE sufficiently discomforting to cause interference with usual work activities.

- ***Severe (Grade 3):*** AE that is incapacitating, with inability to work or perform daily activities.
- ***Life-Threatening (Grade 4):*** AE that is potentially life threatening.
- ***Death (Grade 5):*** Death related to AE.

8.2.2. Grading of Laboratory Safety Tests for Reporting and Analysis

Treatment-emergent abnormal laboratory results will be reported as AEs when assessed as "clinically significant" using the procedures and criteria detailed in Section 8.1.5.

For purposes of analyzing laboratory data, all laboratory results will be graded using NCI CTCAE v4.03 and then summarized as "shift tables" comparing baseline and treatment-emergent results. This process will assure that the final study report contains complete and consistent analyses of safety laboratory tests.

8.2.3. Relationship to Study Drug

This determination is based on the Investigator's clinical judgment regarding the likelihood that the study drug caused the AE and may include consideration of some or all of the following factors:

- Alternative possible causes of the AE, including the patient's underlying disease or co-morbid conditions, other drugs, other host and environmental factors;
- Temporal sequence between the exposure to study drug and the AE;
- Whether the clinical or laboratory manifestations of the AE are consistent with known actions or toxicity of the study drug;
- Whether the AE resolved or improved with decreasing the dose or stopping the study drug (i.e., dechallenge); or recurred or worsened with re-exposure to the drug (i.e., rechallenge).

The relationship between the study drug and the AE will be described using one of the following categories:

- ***Related:*** the study drug is more likely the cause of the AE than other factors;
- ***Possibly related:*** there is a *reasonable* possibility that the study drug is the cause of the AE, including that the study drug and another factor(s) are equally likely as causes of the AE;
- ***Unlikely related:*** another factor is considered more likely the cause of the AE than the study drug;
- ***Not related:*** another factor is considered to be the cause of the AE.

Related and possibly related AEs may result during the use of the study drug as planned (per protocol), or from abuse, withdrawal or over-dosage of the agent.

8.2.4. Expectedness

AEs meeting the criteria in Section 8.1.4 are to be considered unexpected.

8.2.5. Date and Time of Onset

The date and time at which the event was first apparent. Table 8-1 summarizes the basis for reporting the date and time of onset for the different types of AEs.

Table 8-1: Reporting the Date and Time of Onset of AE for Different Types of Events

Type of Event	Examples	Source of Date and Time of Onset
Symptom	Headache, feverish, paresthesia	When first experienced by the patient
Sign (Finding)	Elevated BP, enlarged liver on physical exam	When first observed by the Investigator or other study staff
Laboratory / diagnostic result	Neutropenia, hyperglycemia, lesions on brain scan	When laboratory sample was obtained or diagnostic study performed

The time of onset of symptoms may be appreciably earlier than the date and time the Investigator becomes aware of the event. Some events may be apparent to the patient and Investigator independently, and information from each may contribute to the final report. For example, a patient may report the onset of a rash two days before being seen by a physician who makes a diagnosis of herpes zoster based on appearance and laboratory confirmation. In that case, there is a single AE, with the date of onset based on the date of the initial observation by the patient and a specific description (herpes zoster) based on the clinical examination and tests.

8.2.6. Actions Taken for Management of AE

AEs will be followed and managed by the Investigator, including obtaining any supplemental studies needed to define the nature and/or cause of the event (e.g., laboratory tests, diagnostic procedures, consultation with other health care professionals).

For each AE the Investigator will categorize as follows the actions taken to manage the AE:

- Concomitant medication — one or more medications (prescription or over-the-counter) were started or increased in dose; non-medication actions may also have been ordered.
- Other action — only non-medication action(s) were ordered as management of the AE (e.g., bed placed in Trendelenburg position, warm compresses applied to IV access site).
- No action — no actions were ordered for management of the AE.

8.2.7. Follow-up and Outcome of AEs

If possible, AEs will be followed until resolved (synonyms: recovered, recuperated, ended) either with or without sequelae, including for patients who prematurely discontinue study participation. For AEs that are assessed as not drug-related and are not resolved at the EOS visit, follow-up may be limited with the approval of the Medical Monitor.

The outcome of each event will be described using the following categories:

- Resolved without sequelae — the event resolved and patient returned to baseline;
- Resolved with sequelae — the event resolved but the patient is left with residual problems (e.g., functional deficits, pain);
- Resolving — at the last observation, the event was improving;
- Not Resolved — at the last observation, the event was unchanged;
- Death (Fatal) — to be used for the one AE which, in the judgment of the Investigator, was the primary cause of death;
- Unknown — there were no observations after the onset (initial observation or report) of the event.

Note: Resolving and Not Resolved may also be used for AEs that were unresolved at the time a patient died, but were *not* assessed as the primary cause of death.

8.2.8. Date and Time of Outcome

For each class of outcome as defined above, Table 8-2 indicates the date and time to be recorded. As discussed in detail for date / time of onset (see Section 8.2.5), determining the date / time an event resolved (ended) should reflect the type of event and the source of the information.

Table 8-2: Date and Time of Outcome for AE by Outcome Class

Outcome assigned to AE	Date and Time to be Recorded
Resolved (with or without sequelae)	Date and time event observed or reported as resolved
Death	Date and time of death
Resolving or Not Resolved	Date and time of last observation
Unknown	None (see definition above)

8.3. Time Period and Frequency for Event Assessment and Follow-Up

Procedures for the collection and recording of AEs are as follows:

- From obtaining informed consent through EOS, there will be active surveillance to identify all AEs. Events will be recorded in the AE portion of the eCRF, with particular

attention to whether the onset of the event was before or after the administration of the first dose of study drug.

- After EOS, surveillance will be passive (only events brought to the Investigator's attention will be considered) and only events assessed as SUSARs (see Section 8.1.4) will be recorded.

8.4. Reporting Procedures

8.4.1. Adverse Event Reporting

Each patient must be carefully monitored for the development of any AEs. This information should be obtained in the form of non-leading questions (e.g., "How are you feeling?") and from signs and symptoms detected during each examination, observations of study personnel, and spontaneous reports from patients.

All AEs (serious and non-serious) spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures occurring within the time frame specified in Section 8.3 will be documented in the patient's source documents and recorded in the eCRF. Any clinically relevant (as determined by the Investigator) deterioration in laboratory assessments or other clinical findings is considered an AE and must be recorded in the patient's source documents and in the eCRF.

The AE term should be reported in standard medical terminology when possible. Also when possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. For each AE, the investigator will evaluate and report the onset, resolution, intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the patient to discontinue the study.

8.4.2. Serious Adverse Event Reporting

SAE reporting, including supporting materials, will be performed by the site using a system approved by the Sponsor; detailed training will be provided during site initiation. Contact information for guidance and assistance with SAE reporting will be provided in the study operational manual.

8.4.2.1. Procedures for Reporting SAEs to the Sponsor

The ***initial notification*** of each SAE will be reported within 24 hours of the time the Investigator (or the Investigator's designee) becomes aware that the event has occurred and will include the following items of information (any items not available should be explicitly noted):

- Protocol number, study site, patient number;
- Investigator's name, address, and contact information (phone, fax, email);

- Description of the event (i.e., date and time of onset, initial assessment, treatments and course);
- Current status of the patient and the event;
- Criteria by which the event was assessed as serious;
- Date of the first administration of study drug;
- Date of the last administration of study drug prior the event;
- Assessment of relationship of study drug to the event;
- Whether the study drug was discontinued or adjusted as a result of the event.

A ***narrative summary*** of the event will be reported within 2 days for death and life-threatening events and within four days for all other SAEs. The narrative summary will include specific information that will assist in understanding the event, e.g., relevant medical history, co-morbid conditions, physical exam, diagnostics, assessment, treatments (including concomitant medications), response to treatment, course, and outcome (if known).

Thereafter, signed ***supplemental (follow-up) information*** will be provided as it becomes available to the Investigator (either directly or as a result of investigation into a query). Such information includes but is not limited to:

- Copies of relevant medical reports — including diagnostic procedures (e.g., laboratory tests), surgical procedures, and consultations
- More definitive outcome for events previously reported as ongoing or unknown outcome

8.4.2.2. Requirements for Expedited and Periodic Reporting of Adverse Events

SUSARs are required to be reported rapidly to regulatory authorities and to IRB/IECs (typically within 7 days for fatal or life-threatening SUSARs; within 14 days for all other SUSARs). The Sponsor and the Investigator will work together to meet these reporting requirements.

8.4.2.3. Notification of SAEs to the Investigator by the Sponsor

In accordance with regulatory requirements, the Sponsor will notify the Investigator of the occurrence of SUSARs reported by other Investigators in this or in other studies involving the study drug. The Investigator will promptly inform his/her IRB/IEC of such communications from the Sponsor and will document that notification in the Investigator's Regulatory Binder.

8.4.3. Events of Special Interest

None.

8.4.4. Reporting of Pregnancy

Pregnancies occurring in the patient or patient's partner while the patient is receiving study drug or within 1 month after the patient's last dose of study drug will not be considered serious, but are to be reported using the same procedures as for SAEs described in Section 8.4.2.

Study drug must be discontinued immediately in the event of a pregnancy in the patient. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the patient / patient's partner until completion of the pregnancy, and must notify the Medical Monitor of the outcome within 5 days. The Investigator will provide this information as a follow-up to the initial report.

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), then the Investigator should report it as such. Furthermore, all neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator suspects is related to the in utero exposure to the study drug should also be reported.

8.5. Study Halting Rules

Stopping Rules may be developed if unexpected SAEs with causal relationship to study drug, including delivery procedure, appear during the study.

The study also may be stopped based on a decision on the part of the Sponsor to suspend or discontinue development of study drug.

8.6. Safety Oversight

Table 8-3 indicates specific procedures in this protocol for managing these previously identified risks.

Table 8-3: Monitoring Procedures for Risks Identified in Prior Studies of X4P-001 (AMD11070)

Prior Findings	Clinical Monitoring Procedures
X4P-001 is predominantly metabolized through CYP3A4[1]	Avoid concomitant medications that are strong CYP-3A4 inhibitors or inducers; if a strong inhibitor or inducer cannot be avoided, the dose of X4P-001 can be reduced with approval of Medical Monitor.
X4P-001 is a moderate inhibitor of CYP2D6[1]	Avoid sensitive CYP2D6 substrates. Closely monitor other concomitant medications CYP-2D6 substrates.
Beagles, 13-week toxicology study with X4P-001 (free-base)[2] -- ALT: mild (1.4x–2.4x), exposure-related increases -- Total bilirubin: no increases in any animal -- Microscopic liver findings: multifocal necrosis (single cell) in 4 of 12 animals dosed at 35 or 70 mg/kg/d	Safety laboratory tests, including aspartate transaminase, alanine transaminase, total bilirubin, every 4 weeks during treatment.
Rats, 26-week toxicology study with AMD11070PHB (salt)[3] -- retinal degeneration (20, 50, 100 mg/kg bid) -- retinal atrophy (100 mg/kg BID only)	An ophthalmology evaluation every 12 weeks: visual acuity assessment; color vision assessment; slit lamp exam; retinal examination with photographs.

1. A detailed listing of agents with potential for CYP-related interaction is provided in Appendix Section 18.2.
2. The liver findings in beagles treated for 13 weeks with the PHB salt were greater than those observed with the free base drug. This (and all prior) clinical studies use only the free base drug.
3. The retinal changes were observed only in albino rats treated for 26 weeks with the PHB salt. No retinal changes were observed in beagles treated for 13 weeks with either the free base or the PHB salt.

8.6.1. Additional Procedures for Monitoring Patient Safety

Additional procedures for patient safety are summarized below; a detailed schedule of assessments is presented in Table 1-1.

- The first dose of study drug will be administered by study personnel. Patients will then be observed for at least 1 hour before receiving nivolumab (typically a 1 hour infusion), and then observed for at least one hour post-infusion.
- Ongoing monitoring for AEs.
- Regularly scheduled safety laboratory tests.
- Ongoing monitoring of all concomitant medications (prescription and over-the-counter) to avoid potential DDIs mediated through alterations in CYP-metabolism
- Detailed procedures for monitoring and review of data, including DRC meetings (see Section 8.6.2) and regularly scheduled teleconferences including active Investigators, the Medical Monitor, and the Sponsor, to discuss overall clinical experience including safety and outcomes.
- Detailed provisions (summarized below) for management of study drug in individual patients based on safety and tolerability (see Section 5.6), and on disease response (see Sections 5.7 and 7.1.4.2).

8.6.2. Data Review Committee (DRC)

A DRC will be convened to assess the safety of the combination of X4P-001 and nivolumab. The details of the review procedures will be documented in a DRC charter.

Members of the DRC will have appropriate experience treating patients with advanced ccRCC and/or conducting early phase studies of investigational drugs and will include the following:

- The medical monitor for the study.
- Participating Investigators.
- A physician representative of the Sponsor.

The first formal DRC review of safety data will occur after 3 patients have completed 28 days (Cycle 1) of treatment or discontinued prematurely due to an AE. The DRC will be presented all available safety data and will be expected, based on their judgment, to make a specific recommendation for the progress of the study, that is, to continue enrollment, to stop enrollment, or to conduct a second safety review after an additional 3 patients complete Cycle 1.

To further protect patients' safety, TLTs will continue to be monitored during the remainder of the study, including a second formal DRC review of all available safety data after 12 patients have completed 28 days (Cycle 1) of treatment or discontinued prematurely due to an AE. Specifically, if less than or equal to 4 TLTs are observed in the first 12 patients, the trial will continue with the same dose level for the remaining patients. If 5 or more TLTs are observed, the trial may continue with dose de-escalation, i.e., the rest of the patients will be dosed at 200 mg QD. If excessive TLTs are observed anytime during the trial, a dose de-escalation can be enforced following DRC review or the trial can be stopped at the sponsor's discretion.

9. CLINICAL MONITORING

9.1. External Review of the Study Conduct at Participating Sites

All study-related materials at the site are subject to external review to ensure the safety of the patients, the integrity of the study data, and compliance with all applicable regulatory and oversight requirements.

There are several different classes of review:

- Monitoring — review by the Sponsor or authorized representatives, typically from the contract research organization (CRO) coordinating the clinical conduct of the study. As detailed below, visits may be conducted before, during, and after the conduct of the study.
- Audits — systematic, independent review by the quality assurance department of the Sponsor or authorized representatives, potentially from an organization not involved in the clinical conduct of the study;
- Regulatory review — performed by representatives of regulatory authorities with responsibility for oversight of the study or approval of the investigational agent. These authorities may be from the country where the site is located or from another country.

Monitoring and auditing visits on behalf of the Sponsor will be scheduled with the Investigator in advance and will be conducted at a reasonable time. To facilitate these visits, the Investigator will assure that the following are available:

- Appropriate space, facilities and access to all source documents (including access to computerized records either electronically or as complete print outs).
- Consent/assent forms, eCRFs, SAE forms, and medical records for all screened and enrolled patients.
- Timely access to site personnel, including the Investigator, sub Investigator(s), and other study personnel on the day of the visit to resolve any questions that arise.

Regulatory authorities may visit and review the site and/or Investigator during or after the study and may or may not notify the Investigator or the Sponsor in advance. The Investigator will fully cooperate with regulatory audits conducted at a reasonable time in a reasonable manner. The Investigator will notify the Sponsor immediately of any contact by or communication from regulatory authorities regarding the study.

9.2. Study Monitoring Visits

9.2.1. Site Qualification and Initiation Visits

Before an investigational site can enter a patient into the study, a representative of X4 will visit the site to perform the following:

- Inspect the facilities (e.g., clinical and administrative areas, pharmacy, laboratory).
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, as well as the responsibilities of X4 and its representatives.
- Review the site trial master file (TMF), including documentation related to the protocol, the Investigator, and other study site personnel; correspondence to and from the IRB/IEC, the Sponsor, and their representatives.
- Review the standard operating procedures and current practices relating to clinical and pharmacy activities, data handling, the IRB/IEC oversight and the informed consent process.

9.2.2. Interim Monitoring Visits

During the study, a CRA from or representing X4 will visit the investigational site, for the following:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product is being appropriately handled and accounted.
- Perform source data verification, including verifying the data in the eCRFs against the relevant source documents (see Section 11.3) and resolving any discrepancies noted.
- Record and report any protocol deviations.
- Confirm that AEs and SAEs have been properly documented on eCRFs; that any SAEs have been forwarded to X4; and that SAEs meeting criteria for reporting have been forwarded to the IRB/IEC.

Between visits the CRA will be available as needed to provide information or support to the Investigator(s) or other staff.

9.2.3. Study Closeout Visit

The study will be considered complete when all of the following have occurred:

- All treated patients have completed all scheduled visits plus any unscheduled follow-up required by AEs;
- All eCRFs have been completed, submitted and all queries resolved;
- The study database has been locked.
- The Sponsor or designee will then conduct a study closeout visit, which may include, but is not limited to, the following:
- Review the site TMF to assure all required regulatory documents are current and complete.
- Resolve any open issues from prior monitoring, audit or inspection visits.
- Review the site's provisions for meeting the requirements for retention study records.
- Discuss possible future site audits.
- Review the Sponsor's publication policy.
- Confirm compliance with requirements for notifying the IRB/IEC of study events, including closure.
- Collect any unused study materials for either return to the Sponsor or disposal in a manner approved by the Sponsor.

10. STATISTICAL CONSIDERATIONS

10.1. Statistical and Analytical Plans

A detailed statistical analysis plan (SAP) will be developed. The SAP will define populations for analysis, outline all data handling conventions, including software, and specify additional statistical methods to be used for analysis of safety, efficacy and pharmacokinetics.

10.2. Statistical Hypotheses

Not applicable.

10.3. Analysis Datasets

Analyses will be performed using the following populations:

- Safety Population — all patients who received at least one dose of study drug.
- Intent-to-Treat (ITT) Population — all patients who received at least one dose of study drug

  Clinically Evaluable (CE) Population – all patients who have adequate data at baseline and at one or more post-treatment tumor assessment, and no major protocol deviations. The clinically evaluable population may be omitted from the final analysis if the clinically evaluable population and ITT populations if there are no clinically meaningful differences in outcomes between the 2 populations.

10.4. Description of Statistical Methods

10.4.1. General Approach

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 *last* 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 hour after dosing is designated t = 2 h.

Missing data will not be imputed. Further details for handling of missing, duplicated or unscheduled data will be given in the SAP.

If changes are made to the SAP, then these will be listed in the Clinical Study Report (CSR), along with an explanation as to why they occurred.

10.4.2. Baseline Descriptive Statistics

10.4.2.1. Disposition

The number of patients who were in each analysis population, the number who received any study drug, the number who completed the study, and the reasons for treatment discontinuation will be summarized. A by-patient listing of study completion information, including the reason for premature study withdrawal will be presented.

10.4.2.2. Demographics and Medical History

Disease history, baseline medical history, and demographic variables will be summarized using descriptive statistics (n, mean, standard deviation, median, range) for continuous variables and frequency and proportion for categorical variables.

10.4.3. Analyses of Safety Data

The primary objective of the study is safety and tolerability. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 16.0 (or later) and tabulated by system organ class and preferred term, severity, and relationship to study therapy. TLT events will be summarized.

Safety observations will be analyzed using descriptive statistics and tabulation. No formal statistical comparisons are planned. All safety data will be presented in listings.

The incidence of treatment emergent adverse events (defined as events occurring on or after the first dose of study treatment through 30 days after the last dose), grade 3 or higher events, treatment-related events (defined as events indicated as possibly related or related to either study drug), TLTs, events leading to study discontinuation, and events leading to dose modifications, will be summarized by system organ class and preferred term for the safety population. Events will also be summarized by maximum severity and relationship. By-patient listings will be provided for deaths, SAEs, TLTs, and AEs leading to discontinuation of treatment.

Vitals signs, quantitative laboratory tests, and quantitative ECG intervals will be summarized using descriptive statistics as reported value and change from baseline by timepoint. ECOG will be presented as a shift from baseline to the last value on study and the worst value on study. Laboratory tests with CTCAE grading (v 4.03) will be summarized by shifts from baseline to the

last grade and worst grade on study. Laboratory values without grades will be summarized as shifts from below, within, and above normal ranges by timepoint. Ophthalmologic examinations and physical examination data will be listed.

Exposure to nivolumab and X4P-001 will be summarized and parameters will include duration of treatment, number of doses of each therapy received, the incidence of patients who had dosing held or permanently discontinued.

Concomitant medications will be listed by patient, medication start and stop dates and medication name.

10.4.4. Planned Interim Analyses

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

10.4.5. Analyses of the Efficacy Endpoints

Antitumor activity will be evaluated using RECIST v1.1 [Eisenhauer 2009], to determine the following metrics:

- Objective response rate (ORR), where response is defined as achieving either CR or PR.
- Time to objective response
- Duration of objective response
- Disease control rate (DCR; CR+PR+SD)
- PFS, defined as the time from first administration of combination regimen until objective tumor progression or death from any cause.
- TTP, defined as the time from first administration of combination regimen until objective tumor progression (excluding deaths)

Best response per RECIST v1.1 and ORR will be summarized. Patients who do not have data sufficient for response assessment will be considered treatment failures. The number and proportions of responders will be summarized as a percent of the analysis population. ITT will be the primary population for analysis and the CE population will be considered supportive.

Disease control rate will be calculated as the number of patients who had CR, PR, or SD at 16 weeks and 24 weeks divided by the ITT population.

PFS, duration of response, and TTP will be summarized using Kaplan Meier methods. Median, 25^{th}, and 75^{th} percentiles will be reported.

PFS will be calculated from the date of first dose to the time of documented PD or death due to any cause. Patients who are still alive and have not had PD at the data cutoff for the final efficacy analysis, or who drop out prior to study end, will be censored at the date of last tumor assessment that the patient was progression-free on or prior to the data cutoff. If a patient begins a new anti-

cancer therapy prior to documented PD (or death), the patient will be censored at the date of last assessment when the patient was documented as progression-free prior to the intervention. Patients with two or more consecutive missing response assessments prior to a visit with documented progression (or death) will be censored at the last date of tumor assessment when the patient was documented to be progression free. Patients who do not have any response assessments and have not died will be censored on the day of first dose.

The median duration of PFS will be estimated based on the 50th percentile of the Kaplan-Meier distribution; additional summary statistics will be presented, including the 25th and 75th percentiles, 95% confidence intervals on the median, and proportion of censored data. Further details regarding censoring will be described in the SAP.

Duration of response will be calculated from the date of first response (CR or PR) to the date of documented PD for the subset of patients who had a best response of CR or PR.

TTP will be calculated from the first dose date until the date of documented PD for all patients. TTP and duration of response will use Kaplan-Meier methods in the same manner as the analysis of PFS and will be described in the SAP.

Tumor Response and endpoints listed above may also be explored by using the iRECIST [Seymour 2017]. Details of the analysis will be defined in SAP.

10.4.6. Multiple Comparison/Multiplicity

Not applicable.

10.4.7. Tabulation of Individual Response Data

The individual response data will be tabulated and the details will be described in SAP.

10.4.8. Exploratory Analyses

The details of exploratory analyses will be described in SAP.

10.4.9. Pharmacokinetic Analyses.

PK data will be analyzed using descriptive statistics for AUC, C_{max}, and T_{max}.

10.5. Sample Size

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.

Dose de-escalation may occur during the study if excessive TLT is observed (see Section 8.6.2). With the de-escalation rule, the trial with a higher TLT rate at the starting dose (400 mg QD) will increase the probability of the de-escalation to protect patients' safety. For instance, if the TLT rate in the first 12 patients is 30%, the probability of de-escalation is 28%; if the TLT rate is 40%, the probability of de-escalation is 56%; if the TLT rate is 50%, the probability of de-escalation is 81%.The de-escalation rule will serve as statistical guidance.

10.6. Measures to Minimize Bias

10.6.1. Enrollment/ Randomization/ Masking Procedures

All patients will be treated open-label; no blinding methods will be employed.

10.6.2. Evaluation of Success of Blinding

Not applicable.

10.6.3. Breaking the Study Blind/Participant Code

Not applicable.

11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Source documents are the originals of any documents used by the Investigator, hospital, or institution that verify the existence of the patient and substantiate the integrity of the data collected during the study.

11.1. Medical Records

Medical records related to the patient's routine clinical care, including prior to or during the study:

- Information obtained from the patient's personal physicians or other third parties regarding the patient's medical history or prior physical condition.
- Medication prescription and administration records.
- Laboratory reports, including clinical pathology and diagnostic histologic pathology.
- Reports of imaging studies.
- Data and reports from automated instruments (e.g., vital signs).
- Medical records relating to scheduled and unscheduled clinical visits

11.2. Study-Specific Source Documents

Study-specific source documents include, but are not limited to, the following:

- The informed consent form, signed and dated by the patient.
- The site screening log.
- Any clinical reports noted above that are scheduled as part of the protocol and have been annotated to indicate the significance of any abnormal findings.
- Concomitant medication prescription and administration records.
- Records relating to scheduled and unscheduled study visits, including, but not limited to, results of examinations, observations relating to AEs, and concomitant medications.

11.3. Source Documents Requirements

The following document characteristics are essential to assuring data quality and are required of all documents generated by the Investigator and the study team during the course of the study.

- Be prepared at the time of the events or activities described (i.e., contemporaneously);
- Indicate both the date and time recorded;
- Identify the source of all recorded information (e.g., the patient, direct observations of the recorder, laboratory reports, external / historical sources).
- Text should be readable and unambiguous, including application of best medical record practices (e.g., minimal use of abbreviations; proper numerical, dose and posology formats).

Electronic health record (EHR) systems must be compliant with current regulatory requirements for systems containing "protected health information" (PHI), including, but not limited to:

- Security requirements for restricted access and electronic signatures
- Electronic timestamp
- Audit trails for any changes or amendment

Paper documents must meet the following requirements:

- Be written legibly in dark (preferably black) ink, including signature and date.
- Be signed (or initialed), with date and time, by the recorder. The site must maintain a formal log showing for all study personnel printed name, full signatures, and initials.
- In the event that any entry needs to be changed, a single line will be made through the original entry, the correct information entered (or referenced) on the same page, and the action initialed, dated, and (if appropriate) explained. The original entry must not be obscured or obliterated by multiple cross-out, correction fluid or overlay of other material.

Study-specific source document forms created by the site must be reviewed by the Sponsor prior to use.

11.4. Electronic Case Report Forms (eCRFs)

The Sponsor will provide a regulatory-compliant electronic data capture (EDC) system for reporting study data to a central facility holding the study database. All study personnel will be trained on the system and each will have a unique login password and electronic signature.

The Investigator (or qualified sub-Investigator approved by the Sponsor) will review all eCRFs and indicate their concurrence by (electronic) signature.

12. QUALITY ASSURANCE AND QUALITY CONTROL

12.1. Study Monitoring

Monitoring and auditing procedures developed by the Sponsor or designee will be followed, in order to comply with ICH GCP guidelines, as described in Section 9.2.

12.2. Case Report Form Completion

The Sponsor or designee will provide the study centers with eCRFs for each patient.

eCRFs will be completed for each study patient. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the patient's eCRF. Source documentation supporting the eCRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, AEs, and patient status.

The Investigator, or designated representative, should complete the eCRF as soon as possible after information is collected, preferably on the same day that a patient is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

The Investigator must electronically sign and date the Investigator's Statement at the end of the eCRF to endorse the recorded data.

12.3. Computerized Systems / Medical Records as Source Data

All study data recorded on source documents are to be transcribed into the eCRFs. Any electronic study data are to be entered into a secure, validated data processing system and a backup maintained. Any changes to electronic study data will be documented.

12.4. Audits and Inspections

Authorized representatives of Sponsor or designee, a regulatory authority, or IRB/IEC may visit the study center to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH GCP, and any applicable regulatory requirements.

The investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

12.5. Resolution of Deficiencies

The Investigator agrees to take promptly any reasonable steps requested by the Sponsor to resolve any deficiencies identified as a result of monitoring, audits, inspections, protocol

deviations, or review of any other study documentation. Failure to take adequate remedial action can result in suspension or termination of the study at the site.

13. ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1. Ethical Standard

The Sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, the ethical principles stated in the Declaration of Helsinki, and ICH GCP Guideline E6.

ICH GCP Guideline E6 is available at:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf

13.2. Institutional Review Board

The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the patients. The study will only be conducted at study centers where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, informed consent, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB/IEC as appropriate. Written IRB/IEC approval must be received by the Sponsor or designee before a site can enroll any patient into the study.

The Investigator is responsible for informing the IRB/IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB/IEC must approve all advertising used to recruit patients for the study. The protocol (and other amended study documents) must be re-approved by the IRB/IEC upon receipt of amendments and annually, as local regulations require. The Investigator is also responsible for providing the IRB/IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The Sponsor will provide this information to the Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB/IEC according to local regulations and guidelines.

13.3. Informed Consent Process

13.3.1. Consent/assent and Other Informational Documents Provided to Participants

The Investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient

should be given the opportunity to ask questions and allowed time to consider the information provided. This process should be recorded in the patient's source documentation.

The patient's signed and dated informed consent must be obtained before conducting any study procedures. Documentation of the consenting process must be recorded in the patient's source documents.

13.3.2. Consent Procedures and Documentation

The Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the patient, and this must be documented in the patient's source documents.

13.4. Participant and Data Confidentiality

In order to maintain patient privacy, all eCRFs, study drug accountability records, study reports, and communications will identify the patient by initials (as allowed by local regulations) and the assigned patient number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the patient's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

14. DATA HANDLING AND RECORD KEEPING

14.1. Data Collection and Management Responsibilities

All study data recorded on source documents are to be transcribed into the eCRFs. Any electronic study data are to be entered into a secure, validated data processing system and a backup maintained. Any changes to electronic study data will be documented.

14.2. Study Records Retention

The Investigator will maintain all study records according to ICH GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified immediately by telephone or e-mail and the notification confirmed in writing if a custodial change occurs.

14.3. Protocol Deviations

A protocol deviation is defined as an event in which the Investigator or site personnel did not conduct the study according to the Protocol, including compliance requirements and agreements. Guidelines for minor procedural variations (e.g., collection time of blood samples) will be agreed to and documented by the Investigator and the Sponsor prior to starting the study. Events conforming to those guidelines will not be considered deviations.

For protocol deviations relating to individual patients, the event and relevant circumstances will be recorded on source documents and on the appropriate eCRF; reported to the Sponsor in a timely manner; and presented in the Clinical Study Report.

Deviations that are not patient-specific (e.g., unauthorized use of an investigational agent outside the protocol, either human administration or laboratory use) will be reported to the Sponsor in writing and copies placed in the TMF.

Deviations that can be anticipated should, if possible, be discussed with the Sponsor before being implemented.

14.4. Publication and Data Sharing Policy

X4 recognizes the importance of communicating the results of scientific studies, including clinical studies, and, therefore, encourages their publication in reputable scientific journals and presentation at seminars or conferences. X4 also has legitimate corporate and shareholder responsibilities, including, but not limited to, protecting confidential information about its proprietary products and obtaining patent protection for its intellectual property.

Therefore, the following procedures apply to any communication (including written, oral, or electronic; manuscript, abstract, other publication, or presentation) of results or information arising from this study (including any ancillary studies involving study patients) to any third parties:

- The proposed communication will be prepared in collaboration with the Sponsor.
- The final proposed version must be submitted to X4 for review and comment at least 30 days prior to presentation, submission for publication or other dissemination.
- In the event X4 reasonably determines that a proposed communication contains confidential or patentable material, they may require either of the following:
  - The material be removed from the communication;
  - The communication be delayed for up to 60 additional days to permit filing the appropriate intellectual property protection.

These procedures apply regardless of whether the study is completed as planned or is terminated prematurely for any reason.

15. STUDY ADMINISTRATION

Key personnel, along with relevant contact information, are provided in the study operational manual.

16. CONFLICT OF INTEREST POLICY

The conflict of interest policy is addressed in the Clinical Trial Agreement.

17. LITERATURE REFERENCES

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18. APPENDICES

18.1. Revision History and Sponsor Signature

The revision history is summarized in Table 18-1. Significant revisions made in each protocol version are provided in a separate Summary of Changes document.

Table 18-1: Protocol Revision History

Ver. No.	Date	Comment
1.0	06 May 2016	Initial submission to FDA
2.0	20 Feb 2017	Re-formatted document; allow patients with history of brain metastases if stable; add stopping rule with DRC review following the first 12 patients; incorporate changes as documented in 13Oct16 NTF; incorporated updates to study drug Reference Safety Information (X4P-001 IBv4 & February 2017 nivolumab USPI)
3.0	05 Jul 2017	Modified exclusion criteria and minor administrative changes

This protocol Version 3.0 has been prepared and approved by the Sponsor.

[redacted]
X4 Pharmaceuticals, Inc.
[redacted]

Signature Date

[redacted]
X4 Pharmaceuticals, Inc.
[redacted]

Signature Date

18.2. Potential CYP-Related Drug-Drug Interactions

Strong CYP3A inhibitor[1]	Strong CYP3A inducer[1]	Moderate CYP3A inhibitor[2]	Moderate CYP3A inducer[2]	CYP2D6 sensitive substrate[1]	CYP2D6 moderate sensitive substrate[2]
boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir and ritonavir, diltiazem, elvitegravir and ritonavir, grapefruit juice, idelalisib, indinavir, itraconazole, ketoconazole, lopinavir and ritonavir, mibefradil, nefazodone, nelfinavir, paritaprevir and ritonavir, ombitasvir and/or dasabuvir, posaconazole, saquinavir, telaprevir, telithromycin, tipranavir and ritonavir, troleandomycin, voriconazole	carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort	amprenavir, aprepitant, atazanavir, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, darunavir and ritonavir, dronedarone, erythromycin, fluconazole, fluvoxamine, fosamprenavir, imatinib, tofisopam, verapamil	bosentan, efavirenz, etravirine, modafinil, nafcillin	atomoxetine, desipramine, dextromethorphan, eliglustat, nebivolol, nortriptyline, perphenazine, pimozide, thioridazine, tolterodine, venlafaxine	amitriptyline, encainide, imipramine, metoprolol, propafenone, propranolol, tramadol, trimipramine

1 Prohibited.
2 Use with Medical Monitor approval only.
Note: This list of drugs may not be a complete list, consultation with the medical monitor is requested for any concerns about concomitant medication use.
Sources:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm
http://labeling.pfizer.com/ShowLabeling.aspx?id=759