CLINICAL STUDY PROTOCOL

Protocol Title: Phase 1/2 Multicenter Trial of ICOS Agonist Monoclonal Antibody (mAb) JTX-2011 Alone and in Combination with Nivolumab, Ipilimumab, or Pembrolizumab in Adult Subjects with Advanced and/or Refractory Solid Tumor Malignancies

Product: JTX-2011

Protocol Number: JTX-2011-101

Protocol Version: 9.1 (Amendment 8): 12 May 2021

IND Number: 127929

Sponsor: Jounce Therapeutics, Inc.
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NCT02904226

The experimental protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the Institutional Review Board and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, the ICH E6 guidelines of Good Clinical Practice, 21 CFR 21.50 Protection of Human Patients and 21 CFR 21.56 Institutional Review Boards, and all applicable regulatory authority requirements.

SPONSOR PROTOCOL APPROVAL PAGE

Phase 1/2 Multicenter Trial of ICOS Agonist Monoclonal Antibody (mAb) JTX-2011 Alone and in Combination with Nivolumab, Ipilimumab, or Pembrolizumab in Adult Subjects with Advanced and/or Refractory Solid Tumor Malignancies

Protocol Number: JTX-2011-101

Approved by:

Sponsor's Responsible Medical Officer:

DocuSigned by:

Signature [redacted]

Date 5/25/2021

INVESTIGATOR SIGNATURE OF AGREEMENT PAGE

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AGREEMENT

CONFIDENTIALITY STATEMENT: This and related documents from Jounce Therapeutics, Inc., contain privileged information that is confidential and may not be disclosed unless such disclosure is required by federal laws or regulations. In any event, persons to whom the information is disclosed must be informed that it is privileged and/or confidential and may not be further disclosed by them. Information from this study may not be reproduced in any form without the written permission of Jounce Therapeutics, Inc.

PROTOCOL COMPLIANCE: The signature of the Principal Investigator below constitutes his/her agreement to comply with the contents of this Protocol and to conduct this study according to Good Clinical Practices (GCP) and applicable requirements.

Principal Investigator's Name	Principal Investigator's Title
Principal Investigator's Address	
Principal Investigator's Signature	Date

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LIST OF TERMS, ACRONYMS, AND ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-Drug Antibody
AE	Adverse Event
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine Transaminase (SGPT)
ALP	Alkaline Phosphatase
ANC	Absolute Neutrophil Count
AST	Aspartate Transaminase (SGOT)
AUC	Area Under the Drug Concentration-Time Curve
B7	Ligand for CD28
BLQ	Below the Limit of Quantitation
BP	Blood Pressure
°C	Degrees Celsius
CD28	Cluster of Differentiation 28
ConMeds	Concomitant Medication
CFR	Code of Federal Regulations
CI	Confidence Interval
C_{max}	Maximum Drug Concentration
C_{min}	Minimum Drug Concentration
CL	Clearance
CR	Complete Response
CRO	Contract Research Organization
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTLA-4	Cytotoxic T-Lymphocyte-Associated Protein 4
DLT	Dose-Limiting Toxicity
dMMR	Mismatch Repair Deficient
EAP	Exploratory Analysis Plan
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR	Epidermal Growth Factor Receptor
EP	European Pharmacopoeia
°F	Degrees Fahrenheit
ER	Estrogen Receptor

Abbreviation	Definition
FDA	Food and Drug Administration (U.S.)
FISH	Fluorescence *in situ* hybridization
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
H or hr	Hour
HED	Human Equivalent Dose
HER2	Human Epidermal Growth Factor 2
HNSCC	Head and Neck Squamous Cell Carcinoma
HR	Heart Rate
ICF	Information and Consent Form
ICH	International Conference on Harmonisation
ICOS	Inducible CO-Stimulator of T cells
ICOSL	ICOS Ligand
IgG1	Immunoglobulin G1
IHC	Immunohistochemical
IND	Investigational New Drug (Application)
IP	Immunophenotyping
irAE	Immune-Related Adverse Event(s)
IRB	Institutional Review Board
irRC	Immune-related Response Criteria
IV	Intravenous
Ipi	Ipilimumab
JP	Japanese Pharmacopoeia
JTXP	Jounce pharmacodynamic biomarker
kg	Kilogram
KO	Knock-out
L	Liter
LLN	Lower Limit of Normal
mAb	Monoclonal Antibody
mCRPC	Metastatic Castration-resistant-Prostate Cancer
MedDRA	Medical Dictionary for Regulatory Activities
m^2	Square Meter
mg	Milligram
Min	Minute
Min/Max	Minimum/Maximum

Abbreviation	Definition
mL	Milliliter
ms or msec	Millisecond
MSI	Microsatellite Instability
MSI-H	Microsatellite Instability-High
MSS	Microsatellite Stable
MTD	Maximum Tolerated Dose
NAb	Neutralizing Antibody
NCI	National Cancer Institute
NF	National Formulary
Nivo	Nivolumab
NOAEL	No Observed Adverse Effect Level
NSCLC	Non-Small Cell Lung Cancer
PBMC	Peripheral Blood Mononuclear Cells
PCR	Polymerase chain reaction
PCWG2	Prostate Cancer Clinical Trials Working Group
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Death-Ligand 1
Pembro	Pembrolizumab
PI	Principal Investigator
PK/PD	Pharmacokinetic/Pharmacodynamics
PI3K	Phosphatidylinositol-3-kinase
PR	Progesterone Receptor
PT	Prothrombin Time
q	Every
q3w	Every three weeks
q6w	Every six weeks
RBC	Red Blood Cells
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase Two Dose
RR	Respiratory Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SpO2	Oxygen Saturation
t_{max}	Time to C_{max}

Abbreviation	Definition
T	Temperature
T-bet	T-box transcription factor TBX21
TE	Target Engagement
TEAEs	Treatment Emergent Adverse Events
Teff	T effector cells
TNBC	Triple Negative Breast Cancer
TPS	Tumor Proportion Score
Treg	T regulatory cells
ULN	Upper Limit of Normal
U.S.	United States
USP	United States Pharmacopoeia
WBC	White Blood Cell
WOCBP	Women of Child-Bearing Potential

ICONIC PART/COHORT NAMING CONVENTIONS

As the ICONIC trial is testing multiple arms (referred to as parts) of JTX-2011 as monotherapy and with multiple combination partners at multiple schedules, the following describes naming conventions for the different parts and the cohorts within them.

The table below details the matching Phase 1 and Phase 2 lettering for JTX-2011 as monotherapy, in combination with nivolumab, etc.

JTX-2011 Dosing As	Phase 1 Part	Phase 2 Part
Monotherapy	A	C
w/ Nivolumab	B	D
w/ Ipilimumab	E	F
w/ Pembrolizumab	G	H

Cohorts within each part contain three characters as identifiers. Using cohorts H31 and C64 as examples, the 1st character is a letter indicating which part of the trial that cohort falls under (H31 and C64). The 2nd character indicates whether JTX-2011 is being dosed every three or six weeks (H31 and C64). The 3rd character indicates the numbered sequence a cohort falls under in that part (H31 and C64). H31 is a q3w cohort in Part H, C64 is a q6w cohort in Part C.

If JTX-2011 is being tested in the same tumor type across multiple schedules, the 3rd character will remain the same across both schedules, regardless of whether or not there are prior cohorts in the sequence. For example, H34 is a q3w gastric cohort while H64 is a q6w gastric cohort, however, there are no other q6w cohorts in Part H, (i.e., H61-H63).

Prior to Version 6.0 of the protocol, cohorts with a zero after the 1st character indicated a q3w dosing schedule (e.g., C01, C02, etc.). For continuity, this naming convention will continue with new q3w cohorts in Part C added as part of this amendment (i.e., C06 and C07).

Of note, Parts A and B both have pharmacokinetic/pharmacodynamic (PK/PD) expansion cohorts which don't follow the naming conventions described above, instead they are labeled as AP1, BP1, etc.

PROTOCOL SYNOPSIS

Study Title:	Phase 1/2 Multicenter Trial of ICOS Agonist Monoclonal Antibody (mAb) JTX-2011 Alone and in Combination with Nivolumab, Ipilimumab, or Pembrolizumab in Adult Subjects with Advanced and/or Refractory Solid Tumor Malignancies
Protocol Number:	JTX-2011-101
Sponsor:	Jounce Therapeutics, Inc.
Phase of Development:	Phase 1/2; First-in-human
Objectives for Phase 1: Parts A, B, E, and G	**Primary Objectives** • Assess the safety and tolerability of JTX-2011 monotherapy (Part A), JTX-2011 in combination with nivolumab (Part B), JTX-2011 in combination with ipilimumab (Part E), and JTX-2011 in combination with pembrolizumab (Part G) in subjects with advanced and/or refractory solid tumor malignancies after single and multiple ascending doses; • Determine the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D) of JTX-2011 (Part A), JTX-2011 in combination with nivolumab (Part B), JTX-2011 in combination with ipilimumab (Part E), and JTX-2011 in combination with pembrolizumab (Part G) in subjects with advanced and/or refractory solid tumor malignancies.
	Secondary Objectives • Assess the pharmacokinetics (PK) and pharmacodynamics (PD) of single and multiple ascending doses of JTX-2011 when administered as monotherapy (Part A), JTX-2011 in combination with nivolumab (Part B), JTX-2011 in combination with ipilimumab (Part E), and JTX-2011 in combination with pembrolizumab (Part G); • Assess the PK of nivolumab when administered in combination with JTX-2011 (Part B); • Assess the PK of ipilimumab when administered in combination with JTX-2011 (Part E); • Assess the PK of pembrolizumab when administered in combination with JTX-2011 (Part G).
	Exploratory Objectives • Evaluate the effect of JTX-2011 monotherapy (Part A), JTX-2011 in combination with nivolumab (Part B), JTX-2011 in combination with

	ipilimumab (Part E), and JTX-2011 in combination with pembrolizumab (Part G) on peripheral blood immune cell markers and gene signatures; • Evaluate efficacy (response rate, duration of response, disease control rate, landmark progression free survival rate, progression free survival, landmark overall survival rate, and overall survivcoal) of JTX-2011 as monotherapy (Part A), JTX-2011 in combination with nivolumab (Part B), JTX-2011 in combination with ipilimumab (Part E), and JTX-2011 in combination with pembrolizumab (Part G) in subjects with advanced and/or refractory solid tumor malignancies; • Examine the correlation between potential predictive biomarkers of response and efficacy (response rate, duration of response, disease control rate, landmark progression free survival rate, progression free survival, landmark overall survival rate, and overall survival); • Examine changes from baseline in gene signatures and immune cell subsets within tumor biopsies after treatment with either JTX-2011 monotherapy or a combination of JTX-2011 with nivolumab (Safety/PK/PD Expansion Cohorts AP1, AP2, BP1, and BP2).
Objectives for Phase 2: Parts C, D, F, and H	**Primary Objectives** • Evaluate preliminary efficacy (response rate, duration of response, disease control rate, landmark progression free survival rate, progression free survival, landmark overall survival rate, and overall survival) of JTX-2011 as monotherapy (Part C), JTX-2011 in combination with nivolumab (Part D), JTX-2011 in combination with ipilimumab (Part F), and JTX-2011 in combination with pembrolizumab (Part H) in subjects with specific advanced and/or refractory solid tumor malignancies; • Part C: Confirm the safety and tolerability of JTX-2011 monotherapy in eight (8) indication-specific groups, each with stratification for ICOS expression based upon the fresh tissue biopsy: C01- head and neck squamous cell carcinoma [HNSCC, dosed q3w]; C02 - non-small cell lung cancer [NSCLC, dosed q3w]; C03 - advanced refractory solid tumors other than those eligible for C01, C02, C04, or C05 (dosed q3w) (*closed to enrollment*); C04 - gastric cancer or gastroesophageal junction adenocarcinoma (dosed q3w); C05 - Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) endometrial cancer (*closed to enrollment*); C06 - triple negative breast cancer (TNBC, dosed q3w); C07 - mesothelioma (dosed q3w); C64 - gastric cancer or gastroesophageal junction adenocarcinoma (dosed q6w); • Part D: Confirm the safety and tolerability of JTX-2011 (dosed q3w) in combination with nivolumab therapy in six (6) indication-specific expansion groups, including 5 groups with stratification for ICOS expression: D01 - HNSCC; D02 - NSCLC; D03 - TNBC; D04 - melanoma (*closed to*

	enrollment); and D05 - gastric cancer; and 1 group without stratification: D06 - MSI-H or dMMR endometrial cancer (*closed to enrollment*); • Part F: Confirm the safety and tolerability of JTX-2011 (dosed q6weeks) in combination with ipilimumab therapy in two (2) indication-specific groups, neither with stratification for ICOS expression: F61 - metastatic castrate-resistant prostate cancer [mCRPC, dosed q6w]; and F62 - melanoma (dosed q6w); • Part H: Confirm the safety and tolerability of JTX-2011 in combination with pembrolizumab therapy in six (6) indication or biomarker-specific groups, each with stratification for ICOS expression based upon the fresh biopsy: H31 - HNSCC (dosed q3w); H32 - NSCLC (dosed q3w); H33 - TNBC (dosed q3w); H34 - gastric cancer or gastroesophageal junction adenocarcinoma (dosed q3w); H35 - MSI-H solid tumors (dosed q3w); H64 - gastric cancer or gastroesophageal junction adenocarcinoma (dosed q6w); • Confirm MTD and the recommended Phase 2 dose (RP2D) of JTX-2011 monotherapy (Part C), JTX-2011 in combination with nivolumab (Part D), JTX-2011 in combination with ipilimumab (Part F), and JTX-2011 in combination with pembrolizumab (Part H).
	Secondary Objectives • Confirm the PK/PD of JTX-2011 when administered as monotherapy (Part C), JTX-2011 in combination with nivolumab (Part D), JTX-2011 in combination with ipilimumab (Part F), and JTX-2011 in combination with pembrolizumab (Part H); • Confirm the PK of ni volumab when administered in combination with JTX-2011 (Part D); • Confirm the PK of ipilimumab when administered in combination with JTX-2011 (Part F); • Confirm the PK of pembrolizumab when administered in combination with JTX-2011 (Part H).
	Exploratory Objectives • Examine the correlation between potential predictive biomarkers of response and efficacy (response rate, duration of response, disease control rate, landmark progression free survival rate, progression free survival, landmark overall survival rate, and overall survival); • Evaluate the effect of JTX-2011 monotherapy (Part C), JTX-2011 in combination with nivolumab (Part D), JTX-2011 in combination with ipilimumab (Part F), and JTX-2011 in combination with pembrolizumab (Part H) on peripheral blood immune cell markers and gene signatures.

	• Examine changes from baseline in gene signatures and immune cell subsets within tumor biopsies after treatment with JTX-2011 monotherapy (Part C) and JTX-2011 in combination with ipilimumab (Part F).
Study Drugs:	• JTX-2011 is a humanized IgG1κ monoclonal antibody that is an agonist of Inducible CO-Stimulator of T cells (ICOS). • Nivolumab, marketed as Opdivo®, is a human IgG4κ anti-PD-1 monoclonal antibody manufactured by Bristol-Myers Squibb. • Ipilimumab, marketed as Yervoy®, is a human IgG1κ cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody manufactured by Bristol-Myers Squibb. • Pembrolizumab, marketed as Keytruda®, is a humanized IgG4κ anti-PD-1 monoclonal antibody manufactured by Merck.
Number of Subjects:	Approximately 498 evaluable subjects will be enrolled, assuming the following: • Part A: A total of 27 subjects were enrolled across six (6) dose levels. An additional 12 subjects were enrolled in the safety and PK/PD data (Safety/PK/PD Expansion Cohorts AP1 and AP2); • Part B: A total of 16 subjects were enrolled across four (4) dose levels. An additional 15 subjects were enrolled in the safety and PK/PD data (Safety/PK/PD Expansion Cohorts BP1 and BP2); • Part C: Approximately fifteen (15) subjects each in cohorts C01-C07 and C64 (approximately 120 subjects); • Part D: Approximately fifteen (15) subjects each in cohorts D01-D06 (approximately 90 subjects). • Part E: Approximately three (3) dose levels with a minimum of 3 or up to 6 subjects per dose level, exclusive of replacement subjects and evaluation of escalation dose levels (approximately 18 subjects); • Part F: Approximately fifteen (15) subjects each in cohorts F61-F62 (approximately 30 subjects); • Part G: Two (2) dose levels with a minimum of 3 or up to 6 subjects, exclusive of replacement subjects and evaluation of escalation dose levels (approximately 12 subjects); • Part H: Approximately fifteen (15) subjects each in cohorts H31, H32, H33, and H35 (approximately 60 subjects) and approximately 49 subjects each in cohorts H34 and H64 (approximately 98 subjects).
Number of Centers:	Approximately 36 sites in North America

Overview of Study Design:	This is a Phase 1/2, open label, multicenter, first-in-human trial to evaluate the safety and tolerability, PK, pharmacodynamics, and preliminary efficacy of the ICOS agonist monoclonal antibody JTX-2011 as monotherapy, in combination with nivolumab, in combination with ipilimumab, and in combination with pembrolizumab in adult subjects with advanced and/or refractory solid tumor malignancies. The study is divided into 8 parts. Subjects may be enrolled into any open cohorts for which they qualify at the discretion of the Investigator. **Phase 1 Parts** **Part A (JTX-2011 Monotherapy Dose Escalation) – Completed Enrollment** Part A comprises escalating doses of JTX-2011 administered intravenously (IV) q3w in consecutive cohorts, plus Safety/PK/PD Expansion cohorts (AP1 and AP2) at each of two or more dose levels. **Part B (JTX-2011 + Nivolumab Combination Dose Escalation) – Completed Enrollment** Part B comprises escalating doses of JTX-2011 in combination with nivolumab (both agents administered IV q3w in consecutive cohorts, plus Safety/PK/PD Expansion Cohorts [BP1 and BP2] at each of two or more dose levels). **Part E (JTX-2011 + Ipilimumab Combination Dose Escalation)** Part E comprises escalating doses of JTX-2011 in combination with ipilimumab in consecutive cohorts (JTX-2011 will be administered IV q6w; ipilimumab will be administered IV q3w for a maximum of 4 doses). **Part G (JTX-2011 + Pembrolizumab Combination Dose Escalation)** Part G comprises JTX-2011 in combination with pembrolizumab (JTX-2011 and pembrolizumab will be administered IV q3w). Subjects in Part G are required to have a fresh tumor biopsy during screening. In situations where archival tissue is not available or biopsies are not feasible (e.g., would expose the subject to unreasonable health risks), one or more of these requirements may be waived after discussion with the Medical Monitor. **Phase 2 Parts** **Part C (JTX-2011 Monotherapy Phase 2)** Part C will include eight (8) cohorts in the indications listed below. Each cohort will enroll approximately 15 subjects per cohort. The JTX-2011 dose in Part C is 0.3 mg/kg at both the q3w and q6w dosing schedule. All subjects must have progressed on or after all approved therapies. If prior therapy included a PD-1 inhibitor, subjects must have progressed after at least 2 months of this therapy. **q3w JTX-2011** o C01: HNSCC; o C02: NSCLC;

	○ C03: Any tumor type other than those eligible for C01, C02, C04, or C05 (*closed to enrollment*); ○ C04: Gastric cancer or gastroesophageal junction adenocarcinoma; ○ C05: MSI-H or dMMR endometrial cancer (*closed to enrollment*); ○ C06: TNBC that is immunotherapy naïve; ○ C07: Mesothelioma that is immunotherapy naïve. **q6w JTX-2011** ○ C64: Gastric cancer or gastroesophageal junction adenocarcinoma. Pre-screening for ICOS will not be required. Subjects in Part C are required to have archival tumor and two fresh tumor biopsies (one during screening and one post-dose between C2D1 and C3D1 for subjects on the JTX-2011 q3w dosing schedule, or between C2D1 and C2D22 for subjects on the JTX-2011 q6w dosing schedule). In situations where archival tissue is not available or biopsies are not feasible (e.g., would expose the subject to unreasonable health risks), one or more of these requirements may be waived after discussion with the Medical Monitor. To complete enrollment in the HNSCC (C01), NSCLC (C02), gastric (C04 and C64), and TNBC (C06), at least 15 assessable pre-treatment fresh biopsies must have been obtained in each cohort, 10 of which must have an ICOS score ≥ 2. To complete enrollment in the mesothelioma cohort (C07), 10 subjects must have enrolled with ICOS ≥ 2 based on archival tissue, rather than fresh tissue. If a subject has progressed in Part C, nivolumab can be added to the subject's treatment regimen after confirmation of progression and at the discretion of the Sponsor and Investigator. After the completion of Part G, instead of nivolumab, pembrolizumab can be added to the subject's treatment regimen upon confirmation of disease progression and at the discretion of the Sponsor and Investigator. Confirmatory scans should be performed no less than 4 weeks from the most recent radiographic assessment documenting disease progression. **Part D (JTX-2011 + Nivolumab Combination Phase 2)** Part D will include six (6) cohorts in the indications listed below of JTX-2011 in combination with nivolumab. The JTX-2011 dose in Part D is 0.3 mg/kg. **q3w JTX-2011 + q3w nivolumab** ○ D01: HNSCC that has progressed on or after a prior PD-1 inhibitor; ○ D02: NSCLC that has progressed on or after a prior PD-1 inhibitor; ○ D03: TNBC; ○ D04: Melanoma that has progressed on or after a prior PD-1 inhibitor (*closed to enrollment*); ○ D05: Gastric cancer or gastroesophageal junction adenocarcinoma; ○ D06: MSI-H or dMMR endometrial cancer (*closed to enrollment*).

	Part F (JTX-2011 + Ipilimumab Combination Phase 2) Part F will include two (2) cohorts in the indications listed below, dosing JTX-2011 in combination with ipilimumab. Each cohort will enroll approximately 15 subjects. The JTX-2011 dose level in Part F will be determined in Part E. **q6w JTX-2011 + up to 4 doses of Ipilimumab (q3w)** o F61: mCRPC that has progressed on or after treatment with at least one prior standard of care therapy; o F62: Unresectable or metastatic melanoma with ≤ 2 prior lines of therapy in the unresectable or metastatic setting. Pre-screening for ICOS will not be required. Subjects in Part F are required to have archival tumor and two fresh tumor biopsies (one during screening and one post-dose between C2D1 and C2D22). In situations where archival tissue is not available or biopsies are not feasible (e.g., would expose the subject to unreasonable health risks), one or more of these requirements may be waived after discussion with the Medical Monitor. To complete enrollment in the Part F cohorts, at least 15 assessable pre-treatment fresh biopsies must have been obtained in each cohort. **Part H (JTX-2011 + Pembrolizumab Combination Phase 2)** Part H will include six (6) cohorts in the indications listed below, dosing JTX-2011 at q3w in combination with pembrolizumab in Cohorts H31-H35 and q6w in combination with pembrolizumab in Cohort H64. Approximately 15 subjects will be enrolled in Cohorts H31-H33 and H35. Cohorts H34 and H64 are expansion cohorts and will each enroll approximately 49 subjects. All subjects must be immunotherapy naïve. **q3w JTX-2011 + q3w Pembrolizumab** o H31: recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy; o H32: metastatic NSCLC that has high PD-L1 expression (TPS Score ≥ 50%) as determined by an FDA-approved test, with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations; o H33: metastatic or recurrent TNBC with ≤ 1 prior line of therapy in the metastatic or recurrent setting o H34: recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma, including adenocarcinoma of the lower esophagus with disease progression on or after 1 prior line of therapy, including human epidermal growth factor 2 (HER2)/neu-targeted therapy, if appropriate; o H35: unresectable or metastatic, MSI-H solid tumors that have progressed on prior FDA-approved treatment and who have no

	satisfactory alternative treatment options or MSI-H colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan; **q6w JTX-2011 + q3w Pembrolizumab** o H64: recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma, including adenocarcinoma of the lower esophagus with disease progression on or after 1 prior line of therapy, including HER2/neu-targeted therapy, if appropriate. Pre-screening for ICOS will not be required. Subjects in Part H are required to have archival tumor and a fresh tumor biopsy during screening. In situations where archival tissue is not available or biopsies are not feasible (e.g., would expose the subject to unreasonable health risks), one or more of these requirements may be waived after discussion with the Medical Monitor. To complete enrollment in the HNSCC (H31), NSCLC (H32), TNBC (H33), and MSI-H solid tumor (H35) cohorts, at least 15 assessable fresh biopsies must have been obtained in each cohort, 10 of which must have an ICOS score ≥ 1. To complete enrollment in the gastric expansion cohorts (H34 and H64), approximately 49 assessable fresh biopsies must be obtained in each, 33 of which must have an ICOS score of ≥ 1.
Study Population:	**Inclusion Criteria** All subjects must meet the following inclusion criteria to be eligible for study participation: 1) Must be willing and able to participate and comply with all trial requirements and able to provide signed and dated informed consent prior to initiation of any trial procedures; 2) **All Parts:** a) Evaluable or measurable disease, according to RECIST v1.1 criteria, with at least one measurable lesion (except for Parts A, B, E and G, see below); b) Meets the requirements for the intended study cohort. 3) **Parts A, B and E Dose Escalation:** Any advanced and/or refractory, non-hematological, extracranial malignancy with disease progression after treatment with all available therapies known to confer clinical benefit. Subjects enrolled to dose escalation cohorts may have evaluable but non-measurable disease. 4) **Parts A and B Safety/PK/PD Expansion Cohorts (AP1, AP2, BP1, and BP2):** a) Any advanced and/or refractory, non-hematological, extracranial malignancy with disease progression after treatment with all available

	therapies known to confer clinical benefit, with ≥ 1 ICOS expression levels as determined by immunohistochemistry on archival tumor or history of documented PD-L1 expression; b) Must have a tumor lesion that can be biopsied at acceptable risk and must agree to both a fresh biopsy between screening and C1D1 and a second biopsy after completion of 2 cycles of study treatment. 5) **Part C** - all subjects must have progressed on or after all approved therapies. If prior therapy included a PD-1 inhibitor, subjects must have progressed after at least 2 months of this therapy: a) C01: HNSCC; b) C02: NSCLC; c) C03: Any advanced, non-hematological, extracranial malignancy other than those eligible for C01, C02, C04, or C05 *(closed to enrollment)*; d) C04 and C64: Gastric or gastroesophageal junction adenocarcinoma, including adenocarcinoma of the lower esophagus. Subjects with HER2 over-expressing tumors must have progressed on or after FDA approved therapy for HER2 over-expressing metastatic gastric or gastroesophageal junction adenocarcinoma; e) C05: Endometrial cancer that is locally determined to have a dMMR as determined by immunohistochemical (IHC) complete loss of expression (absence of nuclear immunoreactivity) of at least one of the mismatch repair genes MSH2, MSH6, MLH1 and PMS2, or to be microsatellite instability-high (MSI-H) by polymerase chain reaction (PCR) *(closed to enrollment)*; f) C06: TNBC that is immunotherapy naïve [negative per American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines for estrogen receptor (ER) protein expression and progesterone receptor (PR) protein expression (< 1% of tumor cell nuclei are immunoreactive), and negative for HER2 protein expression by IHC assay (0 or 1) or by fluorescence *in situ* hybridization (FISH)]; g) C07: Mesothelioma that is immunotherapy naïve; 6) **Part D:** a) D01: HNSCC that progressed on or after at least 2 months of a prior PD-1 inhibitor; b) D02: NSCLC that progressed on or after at least 2 months of a prior PD-1 inhibitor. Subjects with EGFR or ALK genomic tumor aberrations must have progressed on or after FDA approved therapy for these aberrations;

	c) D03: TNBC [negative per ASCO/CAP guidelines for ER protein expression and PR protein expression (< 1% of tumor cell nuclei are immunoreactive), and negative for HER2 protein expression by IHC assay (0 or 1+) or by FISH]; d) D04: Melanoma that progressed on or after at least 2 months of a prior PD-1 inhibitor *(closed to enrollment)*; e) D05: gastric cancer, including subjects with cancer of the gastro-esophageal (G-E) junction. Subjects with HER2 over-expressing tumors must have progressed on or after FDA approved therapy for HER2 over-expressing metastatic gastric or gastroesophageal junction adenocarcinoma; f) D06: Endometrial cancer that is locally determined to have a dMMR as determined by IHC complete loss of expression (absence of nuclear immunoreactivity) of at least 1 of the mismatch repair genes MSH2, MSH6, MLH1 and PMS2, or to be MSI-H by PCR *(closed to enrollment)*; g) If a PD-1 or PD-L1 inhibitor is approved for treatment of TNBC during enrollment of this study, eligibility for subjects within that indication will require progression during or after prior treatment with the approved PD-1 or PD-L1 inhibitor; 7) **Part F:** a) F61: mCRPC that has progressed on or after treatment with at least 1 prior standard of care therapy; b) F62: Unresectable or metastatic melanoma with ≤ 2 prior lines of therapy in the unresectable or metastatic setting; 8) **Part G:** a) Recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy b) Metastatic NSCLC that has high PD-L1 expression (TPS ≥ 50%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations; c) Recurrent or metastatic gastric or gastroesophageal junction adenocarcinoma or adenocarcinoma of the lower esophagus with disease progression on or after one prior line of therapy, including HER2/neu-targeted therapy, if appropriate; d) Recurrent or metastatic MSI-H solid tumors that have progressed on prior FDA-approved treatment and who have no satisfactory alternative treatment options or MSI-H colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

	e) Any advanced and/or refractory, non-hematological, extracranial malignancy with disease progression after treatment with all available therapies known to confer clinical benefit. 9) **Part H** – All subjects must be immunotherapy naïve: a) H31: Recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy; b) H32: Metastatic NSCLC that has high PD-L1 expression (TPS ≥ 50%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations; c) H33: Metastatic or recurrent TNBC [negative per ASCO/CAP guidelines for ER protein expression and PR protein expression (< 1% of tumor cell nuclei are immunoreactive), and negative for HER2 protein expression by IHC assay (0 or 1) or by FISH] with ≤ 1 prior line of therapy in the metastatic or recurrent setting; d) H34 and H64: Recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma including adenocarcinoma of the lower esophagus with disease progression on or after 1 prior line of therapy, including HER2/neu-targeted therapy, if appropriate; e) H35: Recurrent or metastatic MSI-H solid tumors that have progressed on prior FDA-approved treatment and who have no satisfactory alternative treatment options or MSI-H colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan 10) Male or Female ≥ 18 years of age; 11) Have an ECOG performance status 0-1. Subjects with ECOG 2 may be considered for enrollment in Parts C, D, F and H if approved by Medical Monitor; 12) Have a predicted life expectancy of ≥ 3 months; 13) Have the following laboratory values: a) Serum creatinine < 2 × ULN b) Total bilirubin ≤ ULN unless prior history of Gilbert's syndrome; c) Aspartate transaminase and alanine transaminase ≤ 2.5 × ULN; d) Hemoglobin ≥ 9.0 g/dL; e) Platelets ≥ 75×10^9 cells/L; f) Absolute neutrophil count ≥ 1.5×10^9 cells/L (without the use of hematopoietic growth factors). Subjects with lower ANC may be enrolled if not the result of prior therapy, if approved by Medical Monitor; g) Serum albumin ≥ 75% of LLN;

	14) If medical history of the following, case should be reviewed with the Medical Monitor: a) Prior biliary tract disorders (as based on Hepatobiliary SOC high level terms of: obstructive bile duct disorders, hepatic vascular disorders, structural and other bile duct disorders) b) Portal hypertension and/or hepatic vascular disorders 15) Women of child-bearing potential (WOCBP) must have a negative serum pregnancy test at screening and a negative urine pregnancy test prior to administration of each dose of JTX-2011; 16) WOCBP and males with partners of child-bearing potential must agree to use adequate birth control throughout their participation and for 5 months following the last study treatment.
	Exclusion Criteria A subject with any one of the following criteria will not be eligible for study participation: 1) Receiving concurrent anti-cancer treatment (excluding radiation therapy, either approved or investigational, please see Section 3.8.1.1); 2) Have refused standard therapy; 3) Have received anti-cancer therapies listed below within the specified timeframe, or who have ongoing toxicity from prior therapy > Grade 1 according to the Common Terminology for Adverse Events (CTCAE). Exceptions to this are: > Grade 1 toxicities which in the opinion of the Investigator should not exclude the subject (e.g., alopecia, Grade 2 neuropathy, hypo- or hyperthyroidism or other endocrinopathies that are well-controlled with hormone replacement) and are approved by the Medical Monitor: a) Have received biologic therapy, including immunotherapy, < 28 days prior to C1D1; b) Have received a CAR-T therapy; c) Have received chemotherapy < 21 days prior to C1D1, or < 42 days for mitomycin or nitrosoureas; d) Have received targeted small molecule therapy < 14 days prior to C1D1; e) Have undergone organ transplantation including allogeneic or autologous stem-cell transplantation, at any time; 4) Have undergone a major surgery (excluding minor procedures, e.g. placement of vascular access, biopsy, etc.) < 6 weeks prior to the first day of study treatment, C1D1;

	5) Have a history of intolerance, hypersensitivity, or treatment discontinuation due to severe immune adverse events on prior immunotherapy, or documented presence of neutralizing anti-drug antibody to nivolumab (Parts B and D), ipilimumab (Part E and F), or pembrolizumab (Parts G and H). Subjects who discontinued prior immunotherapies for immune-related adverse events that are well-controlled with appropriate treatment may be enrolled if approved by the Medical Monitor; 6) Have a diagnosis of immunodeficiency, either primary or acquired, or treatment with systemic steroids or any other form of immunosuppressive therapy within 7 days prior to C1D1. Exception: inhaled or topical steroids and adrenal replacement doses are permitted in the absence of active autoimmune disease as well as a one-time dose of immunosuppressive agents used prophylactically for contrast allergies; 7) Have any active disease requiring systemic immunosuppressive treatment; 8) Have known severe intolerance to or life-threatening hypersensitivity reactions to humanized monoclonal antibodies or intravenous immunoglobulin preparations; any history of anaphylaxis; prior history of human anti-human antibody response; known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent; 9) Are symptomatic or have uncontrolled brain metastases, leptomeningeal disease, or spinal cord compression not definitively treated with surgery or radiation (brain metastases that are stable and asymptomatic, either treated or untreated, will be allowed); 10) Have current second malignancy at other sites, which requires treatment, or in the judgement of the Investigator, may require treatment within the next year. Concurrent malignancies that do not require treatment and are clinically stable are allowed. A past history of other malignancies is allowed as long as the subject is not receiving specific treatment other than hormonal therapy, and, in the judgement of the Investigator, is unlikely to have a recurrence; 11) Have active and clinically relevant bacterial, fungal, or viral infection, including known Hepatitis A, B, or C or HIV (testing not required); 12) Have received live vaccines within past 30 days (inactivated vaccines are allowed; seasonal vaccines should be up to date prior to first infusion day); 13) Women who are pregnant or breastfeeding; 14) Have experienced symptomatic cardiac disease that is unresponsive to surgical or medical management; 15) Have any medical or social condition that, in the opinion of the Investigator, might place a subject at increased risk, affect compliance, or confound safety or other clinical trial data interpretation.

Dose Escalation Procedure:

A Safety Monitoring Committee (SMC) composed of Investigators, study staff, Medical Monitor, and Sponsor representatives will review and approve all dose escalation decisions in Parts E and G. The SMC will meet after safety data from each cohort of 3 subjects is available to make the decision for dose escalation or de-escalation as described in the following sections.

Dose escalation in Parts A and B have been completed with an RP2D of 0.3 mg/kg q3w in both parts. In Part A, six (6) dose escalation cohorts were explored, 0.003 mg/kg, 0.01 mg/kg, 0.03 mg/kg, 0.1 mg/kg, 0.3 mg/kg, and 1 mg/kg. In Part B, four (4) dose escalation cohorts were explored, 0.01 mg/kg, 0.03 mg/kg, 0.1 mg/kg, and 0.3 mg/kg.

Part E (JTX-2011 + Ipilimumab) and Part G (JTX-2011 + Pembrolizumab) Dose Escalation Schema

Part E Cohort	JTX-2011 Dose (q6w)	Part G Cohort	JTX-2011 Dose (q3w)
E63	0.3 mg/kg	G32	0.3 mg/kg
E62	0.1 mg/kg	G31*	0.1 mg/kg
E61*	0.03 mg/kg	G30	0.03 mg/kg
E60	0.01 mg/kg		

* Starting dose level

In Parts E and G, each dose escalation cohort will consist of a minimum of 3 subjects. The first subject in each dose cohort will receive JTX-2011 + ipilimumab or + pembrolizumab, respectively, on C1D1 (sentinel subject) and be monitored for at least 72 hours as an outpatient until acute and subacute safety is confirmed. If, after 72 hours, there are no safety concerns, the next two subjects in the dose cohort will be allowed to enroll in parallel (if the Investigator and Sponsor agree, then no SMC review will be required). Note: hospitalization is not required.

The first 3 or 6 subjects at each dose-level will be assigned according to the classical 3 + 3 design, as follows. If:

- 0 of 3 subjects in a cohort experiences a DLT, then the next higher dose-level cohort may be enrolled;
- 1 of 3 subjects in a cohort experiences a DLT, then enrollment into that cohort will be expanded to a total of 6 subjects;
- 1 of 6 subjects in an expanded cohort experiences a DLT, then the next higher dose-level cohort may be enrolled;
- >1 of 3-6 subjects in a cohort experience a DLT, then the MTD has been exceeded and further enrollment into that cohort will cease. Using the same criteria, additional cohorts may then be explored until the MTD has been determined, including intermediate doses.

	Subjects in each cohort must complete the first cycle of each cohort through C2D1 assessments or have experienced a DLT to be considered evaluable; non-evaluable subjects will be replaced. Depending upon the dosing schedule being tested in dose escalation, the SMC will review all safety data available through at least 2 weeks (in q3w dosing) or 5 weeks (q6w dosing) and make an initial dose escalation recommendation. Enrollment in the next dose escalation cohort may occur after: • SMC determines that that there are no safety concerns with review of ≥ 14 days data for all evaluable subjects within a cohort; • All subjects within a dose cohort complete ≥ 1 cycle; • DLT observed in < 1 out of 3 evaluable subjects (or < 2 out of 6 evaluable subjects) during Cycle 1; • SMC agrees that no additional subjects are required in the current cohort to further define safety Once an RP2D is determined for a particular part of the trial, subjects at lower doses in that part who remain on study treatment and are tolerating it well may increase their dose to the RP2D. In addition, the SMC will be convened approximately every 3 months to review accumulating safety data and patient disposition by cohort through the duration of the study. **Safety/PK/PD Expansion Cohorts (AP1, AP2, BP1, BP2):** *Completed* At each of 2 or more dose levels, approximately 8 additional subjects will be enrolled for additional safety, PK/PD data. These subjects will be required to have biopsies of their tumors at baseline and after completion of 2 cycles of JTX-2011 for pharmacodynamics assessments. These subjects may be enrolled before, during, and after enrollment has commenced in Part C or D. **First Safety/PK/PD Expansion Cohort**: If safety data are acceptable, Part A Safety/PK/PD Expansion Cohort 1 (AP1) and Part B Safety/PK/PD Expansion Cohort 1 (BP1) will be initiated at the first dose level in that Part at which there is approximately 70% Target Engagement (TE) in 2/3 subjects on Day 8. **Second Safety/PK/PD Expansion Cohort**: If safety data are acceptable, Part A Safety/PK/PD Expansion Cohort 2 (AP2) and Part B Safety/PK/PD Expansion Cohort 2 (BP2) will be initiated at the lowest dose level in that part at which there is approximately 70% TE in 2/3 subjects on Day 21, MTD, or the highest dose studied. **SMC Review:** The SMC may be consulted at the request of either Investigator or Sponsor regarding individual subject continuation beyond the first cycle. Once a RP2D is determined, subjects at lower doses who remain on study treatment and are tolerating it well may increase their dose to the RP2D. The SMC will review safety data as outlined in the dose escalation phase for aggregate AEs for 9 weeks. In addition, the SMC will be convened

	approximately every 3 months to review accumulating safety data and patient disposition by cohort through the duration of the study.
Initiation of Parts C, D, F, and H	**Part C** Assuming that there are no safety concerns in Part A, enrollment in Part C will begin once a dose is identified from Part A that results in approximately 70% sustained ICOS TE through day 21 and PK that support dosing q3w or q6w or the MTD is identified. This is anticipated to be one dose level above the dose level selected for Safety/PK/PD Expansion cohort AP1. **Part D** Assuming that there are no safety concerns in Part B, enrollment in Part D will begin once a dose is identified from Part B that results in approximately 70% sustained ICOS TE and PK that support dosing q3w or the MTD is identified. This is anticipated to be one dose level above the dose level selected for Safety/PK/PD Expansion cohort BP1. **Part F** Enrollment in Part F will begin assuming that there are no safety concerns and the RP2D has been determined from Part E. **Part H** Enrollment in Part H will begin assuming that there are no safety concerns and the RP2D has been confirmed from Part G.
Definition of DLT:	A DLT is defined as any of the following study drug-related toxicities (defined as at least possibly related to study drug) **occurring in the first cycle** of study treatment: Hematological: • ≥ Grade 4 neutropenia lasting > 7 days; • Febrile neutropenia; • Any Grade 3 thrombocytopenia with bleeding or a requirement for platelet transfusions; • ≥ Grade 4 thrombocytopenia (platelets < 25,000/μL). Non-hematological: • AST or ALT > 3 x ULN and concurrent total bilirubin > 2 x ULN without initial findings of cholestasis (e.g., findings consistent with Hy's law or FDA definition of potential drug-induced liver injury [pDILI]); • ≥ Grade 4 AST or ALT of any duration; • Any ≥ Grade 3 non-hematologic toxicity with the following exceptions:

	○ Grade 3 immune-related AE (irAE) that resolves to ≤ Grade 1 or to baseline with immunosuppressive therapy within 3 weeks; ○ Grade 3 fatigue that persists < 7 days; ○ Grade 3 rash that resolves to ≤ Grade 1 within 3 weeks; ○ Grade 3 or 4 elevations in serum amylase and/or lipase that are not associated with clinical or radiographic evidence of pancreatitis; ○ ≥ Grade 3 electrolyte abnormality that lasts < 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical intervention; ○ Grade 3 nausea or vomiting that lasts < 48 hours, and resolves to ≤ Grade 1 either spontaneously or with conventional medical intervention; ○ Grade 3 infusion reaction that resolves within 6 hours to ≤ Grade 1; ○ Alopecia; ○ Grade 3 endocrinopathy that is adequately controlled by hormonal replacement; ○ Grade 3 tumor flare. • Any Grade 4 or 5 Adverse Event (AE); • Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks OR requires systemic treatment; • Any treatment-related Grade 2 or greater toxicity that persists and results in an inability to administer treatment on C2D1. For events that are not included in the above definitions, SMC may declare any additional specific toxicity to be a DLT. If a subject does experience a DLT that subsequently resolves to baseline and does not automatically meet the criteria for study discontinuation the Sponsor in conjunction with the Investigator and/or SMC, may decide if the subject is allowed to stay on treatment and resume treatment at a lower dose.
Definition of MTD:	The MTD is defined as the JTX-2011 dose level that yields the largest estimated toxicity rate below 33%.
Definition of the RP2D:	The RP2D, as well as administration time (currently a one-hour IV infusion each for JTX-2011 and nivolumab, 1.5-hour infusion for ipilimumab, and 30-minute infusion for pembrolizumab) and schedule will be determined in discussion among the Sponsor and Investigators. Observations related to safety, PK,

	pharmacodynamics, and IV infusion tolerability will be included in the rationale supporting the RP2D and schedule.
Duration of Study / Subject Participation:	The total study duration is anticipated to be 24-30 months. Each subject's participation on treatment will last a minimum of approximately 3-4 months, including: • Up to a 28-day screening period; • 1 cycle (3 or 6 weeks) of study treatment. However, subjects may continue to receive additional cycles of study treatment as long as, in the judgement of the Investigator, the subject may be deriving clinical benefit; • End of Treatment visit performed 28 days (± 7 days) after the last dose of study treatment; Once off-treatment, each subject will participate in long-term follow-up. • Long-term follow-up assessments will be done every 12 weeks (±2 weeks) from the last dose of JTX-2011; • All subjects who discontinue study treatment will be followed for: o Survival: Via telephone or email contact until a) death, b) withdrawal of consent, c) they are lost to follow-up, d) the Sponsor notifies sites that survival follow-up is no longer required, or e) termination of study by the Sponsor; o Assessment of treatment-related SAEs until resolution to baseline or Grade 0-1; • Subjects discontinuing treatment due to reasons other than documented disease progression will: Have their tumor assessed (using the same modality that was used during study treatment) every 12 weeks (± 2 weeks) for up to 2 years after the last treatment visit, until a) they start a new therapy for their cancer, b) death, c) withdrawal of consent, d) are lost to follow-up, e) the Sponsor notifies sites that tumor assessment is no longer required during long-term follow-up, or f) termination of study by the Sponsor.
Safety Evaluation:	Safety parameters will include adverse events (AEs), serious adverse events (SAEs), physical examinations, ECGs, vital signs, anti-drug antibodies (ADA) to JTX-2011, nivolumab, ipilimumab, and pembrolizumab, cytokines, and clinical laboratory evaluations. Safety and tolerability will be assessed by the incidence and severity of adverse events as determined by CTCAE v4.03. Immune-related adverse events will also be assessed.
Efficacy Evaluation:	• The anti-tumor activity of study treatment will be assessed using RECIST v1.1 criteria, modified RECIST for subjects with mesothelioma only{Byrne 2004} and Prostate Cancer Clinical Trials Working Group

	(PCWG2) guidelines for subjects with prostate cancer only {Scher 2008} as assessed by study investigators and independent central radiology review. Imaging for efficacy assessments will be performed approximately every 9 weeks with the exception of subjects with prostate cancer who will have imaging assessments every 12 weeks with both computed tomography (CT) and bone scans; prostate cancer outcomes to be assessed per the PCWG2 guidelines. The imaging interval may be increased to every 12 weeks with a +/- 3 week window for subjects who remain on study treatment for ≥ 24 months. . Immune-related response criteria (irRC) {Wolchok 2009} will also be assessed by independent central radiology review as well as study Investigators where feasible.
Pharmaco-kinetic Assessments:	PK assessments for JTX-2011, nivolumab, ipilimumab, and pembrolizumab will be performed.
Biomarkers:	ICOS target engagement (TE), a pharmacodynamic biomarker, will be collected and used to determine RP2D and schedule. Potential predictive biomarkers in tumor specimens, including ICOS IHC, predefined ICOS gene signature, novel gene signature exploration as measured by assays such as Nanostring®, and DNA based assays of mutational burden, will be assessed at baseline and correlated with efficacy outcomes, if sufficient samples are available. Potential predictive biomarkers in peripheral blood, including RNA profiling and DNA based assays of mutational burden, will be assessed at baseline and correlated with efficacy outcomes, if sufficient samples are available. If emerging pharmacodynamic data show that a less frequent sampling schedule is warranted, biomarker sampling may be reduced without a protocol amendment.
Sample Size Determination and Statistical Analyses:	For Part A, Part B, Part E, and Part G, the choice of the number of subjects is based on the classical 3 + 3 design. The approximate sample size in the dose escalation cohorts in Part A will be 36 evaluable subjects, assuming that 6 subjects are assigned at each of 6 planned dose levels. The approximate sample size of the dose escalation cohorts in Part B will be 24 evaluable subjects, assuming that 6 subjects are assigned at each of 4 planned dose levels. The approximate sample size of the dose escalation cohorts in Part E will be 18 evaluable subjects, assuming that 6 subjects are assigned at each of 3 planned dose levels. The approximate sample size of the dose escalation cohorts in Part G will be 12 evaluable subjects, assuming that 6 subjects are assigned at each of 2 planned dose levels.

	Approximately 8 additional subjects will be enrolled in safety/PK/PD expansion cohorts at each of 2 or more dose levels in Parts A (AP1, AP2) and B (BP1, BP2) to obtain additional safety and PK/PD data. Subjects may also be added if exploration of intermediate dose level(s) of JTX-2011 is warranted or if the SMC recommends adding additional subjects at a given dose level to further understand and clarify safety issues. Approximately 120 subjects may be enrolled in Part C (approximately 15 in each cohort). Approximately 90 subjects may be enrolled in Part D (approximately 15 subjects per cohort). Approximately 30 subjects may be enrolled in Part F (approximately 15 subjects per cohort). Approximately 15 subjects may be enrolled in each Part H cohort (assuming 3-6 will be enrolled in Part G). For Part C, Part D, Part F, and Part H, a group sequential design will be used to evaluate the preliminary efficacy of JTX-2011 or JTX-2011 in combination with nivolumab, ipilimumab, or pembrolizumab, with an interim look for futility. A 90% power at a 2-sided α will be achieved for the hypothesis testing by enrolling 15 (Part C) or 15 (Part D, Part F, Part H-except H34 and H64) subjects (no more than 2% of β spent at interim) as the first step, and a potential expansion up to approximately 49 subjects per cohort if the futility boundary is passed based on the result from the first 15 subjects for each cohort. Using the same alpha and a non-binding futility analysis at 40% of evaluable subjects (17) with a Gamma spending function of –3 provides 80% power to rule out 13% in favor of 28%. Results from each part of the trial will be summarized via summary statistics (number, mean, median, standard deviation, quartiles, minimum, maximum for continuous endpoints; number and percent for binary and categorical endpoints). The correlation between efficacy and potential predictive biomarkers will be explored to generate hypotheses for further testing. Detailed statistical analyses will be specified in the Statistical Analysis Plan (SAP) or Exploratory Analysis Plan (EAP).

1 Introduction

1.1. Summary Overview

JTX-2011 is a humanized IgG1κ agonist monoclonal antibody that specifically binds to the Inducible CO-Stimulator of T cells (ICOS), and is designed to generate an anti-tumor immune response through stimulation of T effector (Teff) cells and selective reduction of T regulatory (Treg) cells within tumors. JTX-2011 is being developed in patients with advanced and/or refractory solid tumors who have no standard therapeutic options. The recent development and approvals of immune checkpoint inhibitors have resulted in meaningful clinical benefit for patients and validated the immunotherapeutic approach to cancer, but there is much room for improvement in both development of new treatments and identification of patients most likely to benefit from them.

JTX-2011 is produced in Chinese Hamster Ovary (CHO) cells and supplied as a liquid vial for injection, stored at 2-8°C and soluble in normal saline. It is entering a Phase 1 first-in-human study at a dose of 0.003 mg/kg, administered over 1 hour as an intravenous infusion every 3 weeks. It has been well tolerated in Good Laboratory Practice (GLP) toxicology studies, with a no-observed-adverse-effect-level (NOAEL) of 15 mg/kg in rats and 50 mg/kg in cynomolgus monkeys. The first-in-human dose was selected based on data from multiple sources, with a safety margin of 1000-fold over the maximum dose tested in rats and cynomolgus monkeys. Pharmacodynamic biomarkers have been developed to support selection and optimization of dose and schedule in Phase 1, with a goal of identifying a dose for further development that optimizes efficacy and minimizes toxicity.

Based on extensive evaluation of human tumor specimens and preclinical evaluation in syngeneic mouse tumor models, clinical development of JTX-2011 will incorporate potential predictive biomarkers, designed to prioritize indications and stratify for patients most likely to respond to JTX-2011. Preclinical data indicate that efficacy is correlated with expression of ICOS in tumor infiltrating T cells, with ICOS high tumors having significant and durable responses to JTX-2011 monotherapy. Combination of JTX-2011 with a PD-1 inhibitor results in significant responses even in tumors that are not ICOS high. Additionally, combination of mouse ICOS agonist antibody with a CTLA-4 inhibitor results in significant anti-tumor activity in a preclinical mouse model.

With the incorporation of pharmacodynamics and predictive biomarkers, the goal of JTX-2011 clinical development is to provide meaningful and durable clinical benefit with a manageable safety profile to patients whose cancers are underserved by current therapies.

1.2. Background

JTX-2011 is a humanized IgG1κ agonist monoclonal antibody that specifically binds to ICOS and is designed to generate an anti-tumor immune response through stimulation of Teff cells and selective reduction of Treg cells within tumors. JTX-2011 is being developed in patients with advanced and/or refractory solid tumors who have no standard therapeutic options.

1.3. Rationale for Clinical Development

The approvals of immunotherapeutic checkpoint inhibitors ipilimumab, pembrolizumab, and nivolumab have offered new hope for durable remissions for some patients with advanced, metastatic malignancies such as non-small cell lung cancer (NSCLC), gastric, melanoma, renal cell carcinoma, head and neck squamous cell cancer (HNSCC), classical Hodgkin's lymphoma, hepatocellular cancer, and MSI-H cancers. Patients who achieve complete remission may remain disease-free for years, demonstrating the power of unleashing the immune system to eradicate and prevent recurrence of cancer. Despite these encouraging results, however, only a minority of patients benefit. Attempts have been made to identify patients who are more likely to benefit, and although increased benefit has been demonstrated for programmed cell death protein 1 (PD-1) inhibitors (nivolumab, pembrolizumab) in some patients whose tumors express the PD-1 ligand (PD-L1) {Garon 2015; Topalian 2012} there is clearly much room for improvement in both development of new treatments and identification of patients most likely to benefit from them. These agents have a unique adverse event profile, with immune-related toxicities caused by non-specific immune stimulation in organs not involved by cancer (Opdivo® Full Prescribing Information {Bristol-Myers Squibb Company 2017a}Yervoy® Full Prescribing Information{Bristol-Myers Squibb Company 2017b}, Keytruda® Full Prescribing Information{Merck & Co Inc 2017}).

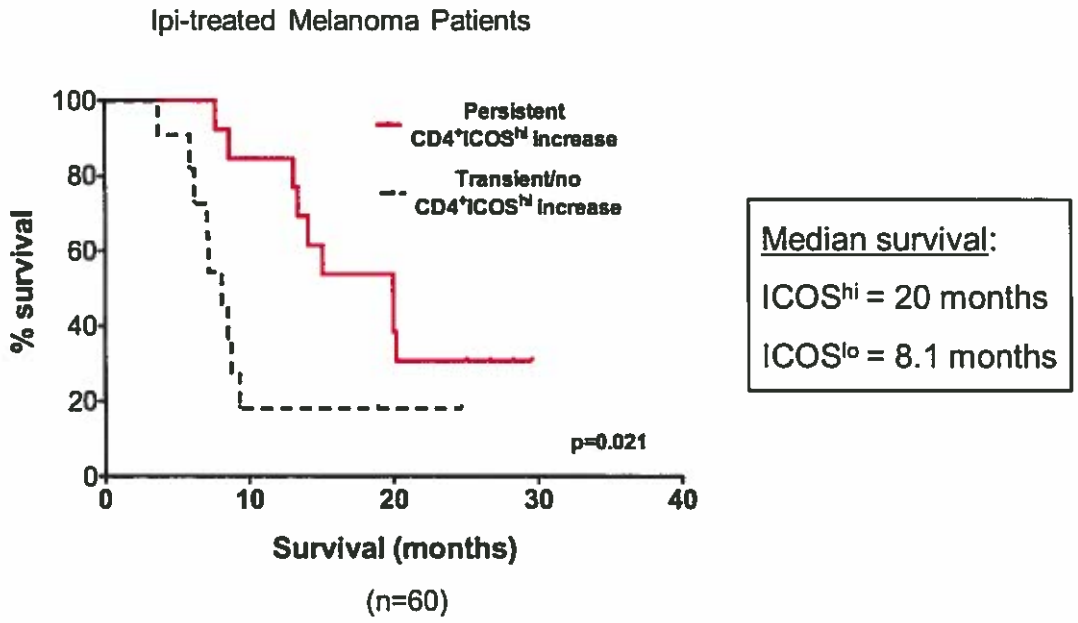
JTX-2011 is a novel ICOS agonist monoclonal antibody being developed in advanced solid tumors to improve outcomes beyond existing immune therapies. Through a dual mechanism of action, JTX-2011 is intended to shift the balance of T cells in a tumor toward anti-tumor activity by stimulation of Teff and depletion of intratumoral Tregs. Predictive biomarkers will be used throughout development to identify patients most likely to respond to JTX-2011.

ICOS is a member of the B7/CD28/CTLA-4 immunoglobulin superfamily and its expression is largely restricted to T cells. Unlike CD28, which is constitutively expressed on T cells and provides co-stimulatory signals necessary for full activation of resting T cells, ICOS is expressed only after initial T cell priming. This biology is an important advantage from a safety perspective. Upon activation, ICOS, a disulfide-linked homodimer, induces a signal through the PI3K and AKT pathways. Subsequent signaling events result in expression of lineage specific transcription factors (e.g., T-bet, GATA-3) and, in turn, effects on T cell proliferation and survival. ICOS has been implicated in diverse aspects of T cell responses {Simpson 2010}. It plays a critical role in the formation of germinal centers, T/B cell collaboration, and immunoglobulin class switching. ICOS-deficient mice show impaired germinal center formation and have decreased production of interleukin IL-10. These defects have been specifically linked to deficiencies in T follicular helper cells. ICOS also plays a role in the development and function of other T cell subsets, including Th1, Th2, and Th17. Notably, ICOS co-stimulates T cell proliferation and cytokine secretion associated with both Th1 and Th2 cells. Accordingly, ICOS knock-out (KO) mice demonstrate impaired development of autoimmune phenotypes in a variety of disease models, including diabetes (Th1), airway inflammation (Th2) and EAE neuro-inflammatory models (Th17). In addition to its role in modulating Teff function, ICOS also modulates Tregs. Notably, ICOS is expressed at high levels on Tregs, and has been implicated in Treg homeostasis and function. Aside from T cells, ICOS has also been shown to be expressed on activated natural killer (NK) cells, where ligation of ICOS may function to increase killing activity {Ogasawara 2002}.

ICOS ligand (ICOSL; B7-H2; B7RP1), also a member of the B7 superfamily, is the only ligand for ICOS and is expressed on the cell surface of B cells, macrophages and dendritic cells. ICOSL functions as a non-covalently linked homodimer and/or a higher order oligomer on the cell surface in its interaction with ICOS {Chattopadhyay 2006}. Notably, human ICOSL, although not mouse ICOSL, has been reported to bind to human and mouse CD28 and CTLA-4 {Yao 2011}, although the functional significance of these interactions has not been elucidated.

ICOS was selected as a therapeutic target based on clinical and nonclinical data suggesting that it plays an important role in the immune response to cancer. Rationale for an ICOS agonist emerged from analysis by the Sharma Lab of patient samples which suggested a role for ICOS in the efficacy of anti-CTLA-4 therapy {Carthon 2010; Chen 2009; Ng Tang 2013}. In a pre-surgical trial in which anti-CTLA-4 (ipilimumab) was administered to bladder cancer patients, the Sharma Lab reported a significant increase in the frequency of ICOS-positive T cells in both tumor tissue and peripheral blood. The Sharma Lab subsequently showed a similar response to anti-CTLA-4 therapy in a cohort of prostate cancer patients. Moreover, the CD4+ ICOS-positive T cells were shown to function as Teff cells, produce IFNγ, and signal via PI3K with an increase in T-bet expression. Of greatest interest, however, was the finding that in melanoma patients treated with ipilimumab, a sustained increase in the frequency of ICOS-positive CD4 T cells correlated with clinical benefit and improved survival (Figure 1). These clinical translational data, which have been confirmed by others {Wang 2012}, suggested that direct agonism of the ICOS pathway might be therapeutically beneficial for patients.

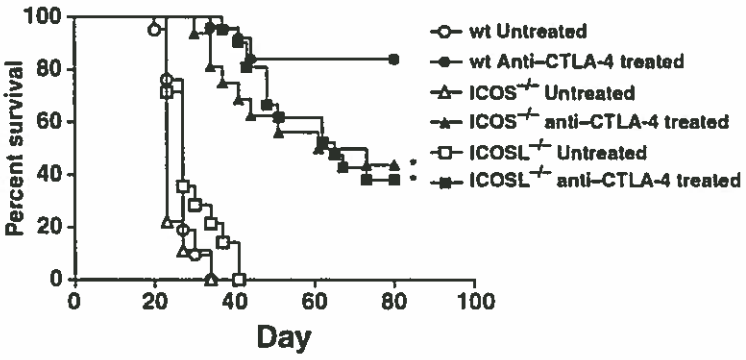
Figure 1: Sustained Upregulation of ICOS Correlates with Survival in Melanoma Patients Treated with Ipilimumab



Kaplan-Meier curve representing 60 melanoma patients treated with ipilimumab shows improved survival for patients with persistent ICOS high CD4+ T cells (personal communication, Dr. Padmanee Sharma, MD Anderson Cancer Center).

To investigate the implications of these intriguing clinical data, the Allison Lab demonstrated that ICOS is critical for optimal response to anti-CTLA-4 in nonclinical models. Mice implanted with B16F10 cells were vaccinated with irradiated B16 tumor cells over-expressing ICOSL (IVAX) in combination with anti-CTLA-4. Those mice receiving the ICOSL containing vaccine plus anti-CTLA-4 showed enhanced survival compared to mice receiving irradiated tumor cells not over-expressing ICOSL combined with anti-CTLA-4. Similar data was observed in a second tumor model, transgenic adenocarcinoma of mouse prostate (TRAMP). Furthermore, optimal efficacy of an anti-CTLA-4 treatment regimen (involving a vaccination approach plus anti-CTLA-4 antibody) in the B16 mouse syngeneic tumor model is abrogated in mice deficient for ICOS or ICOS ligand {Fu 2011}(Figure 2).

Figure 2: Efficacy of anti-CTLA-4 mAb is diminished in mice deficient in ICOS or ICOS Ligand



Anti-CTLA-4 treatment exhibits impaired efficacy in mediating tumor rejection and survival in mice that are deficient in either ICOS or ICOSL.

The role of ICOS in the immune response to cancer does not appear to be limited to the CTLA-4 pathway. ICOS upregulation occurs after treatment with many immune-stimulatory agents, including PD-1 inhibitors {Hirsch 2015}, PD-L1 inhibitors, other co-stimulatory molecules {Hammond 2015; Lambert 2015; Oberst 2015; Redmond 2014}, and vaccines {Mandl 2014; Tiriveedhi 2013}, supporting a combination therapy approach.

Preclinical data suggest that efficacy is correlated with the degree of ICOS expression in tumor infiltrating T cells as measured by immunohistochemistry (IHC). Mouse syngeneic tumor models have demonstrated significant efficacy of JTX-2011 monotherapy in tumors with high baseline ICOS expression. ICOS is upregulated by PD-1 inhibition {JTX-2011 006}, and significant efficacy has been obtained with JTX-2011 in combination with a PD-1 inhibitor in tumors with low ICOS expression that had only a modest response to either JTX-2011 or PD-1 inhibitor alone {JTX-2011 006, JTX-2011 007}.

Table 1: Correlation between ICOS IHC score and efficacy in syngeneic tumor models

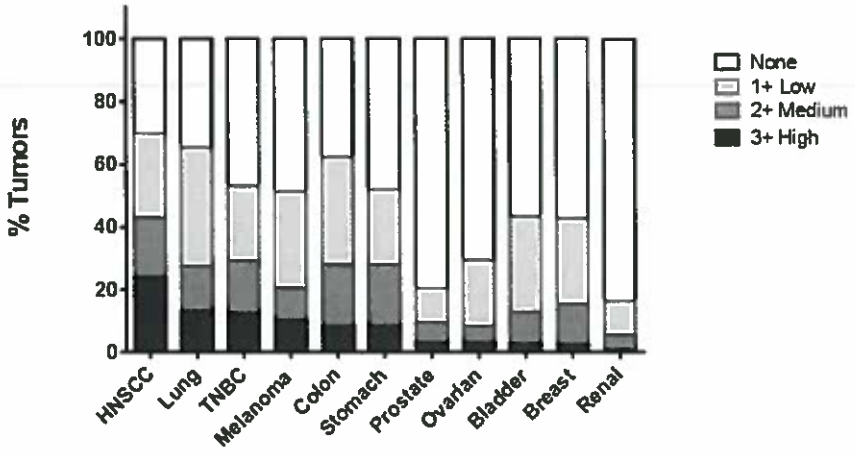
Tumor	ICOS IHC Score	Single Agent Efficacy	Combination Efficacy (+ anti-PD-1)
Sa1/N	3	++++	ND
B16-SIY	2	+++	++++
MC38	1	+	+++
CT26	1	+	++++

{JTX-2011 006, JTX-2011 007}

Recent data emerging from the Allison Lab suggest that anti-PD-1 and anti-CTLA-4 antibodies use distinct cellular mechanisms. In tumor-bearing mice the blockade of CTLA-4, but not PD-1, leads to an increase in ICOS-expressing T effector cells. This result was confirmed in samples from human melanoma subjects {Wei 2017}. The anti-CTLA-4 expansion of an ICOS+ subset of CD4+ Teffs provides a scientific rationale for combining ipilimumab with JTX-2011 and suggests that this combination may be mechanistically distinct from a PD-1 inhibitor plus JTX-2011.

Preclinical data using MC38 tumor-bearing mice genetically modified to express human CTLA-4 demonstrate that the combination of ICOS agonist antibody plus ipilimumab has improved anti-tumor activity compared to either agent alone (Jounce data on file). Combination efficacy in the MC38 model, which has low ICOS expression by IHC as well as low monotherapy efficacy, suggests again that significant combination efficacy may be obtained regardless of ICOS score. Interrogation of human tumor samples has revealed differing patterns of ICOS expression across tumor types, with the highest expression in NSCLC and HNSCC, as shown below (Figure 3) {JTX-2011 013}. Based on the relationship between ICOS expression and efficacy in syngeneic tumor models in mice, patients whose tumor infiltrating lymphocytes express higher levels of ICOS may be more likely to respond to JTX-2011, whereas PD-1 inhibition upregulation of ICOS may result in activity regardless of ICOS expression (Figure 3) {JTX-2011 013}. Based on the relationship between ICOS expression and efficacy in syngeneic tumor models in mice, patients whose tumor infiltrating lymphocytes express higher levels of ICOS may be more likely to respond to JTX-2011, whereas PD-1 inhibition upregulation of ICOS may result in activity regardless of ICOS expression.

Figure 3: ICOS levels by IHC vary across tumor types



A 4-point scoring system based on percentage of ICOS-positive cells was used to classify the samples. The percentage of each tumor type showing 0, 1, 2 or 3 ICOS staining are shown. Tissue microarrays (TMAs) included n=100 tumors per indication with the exception of Melanoma (n=50). {JTX-2011 013}

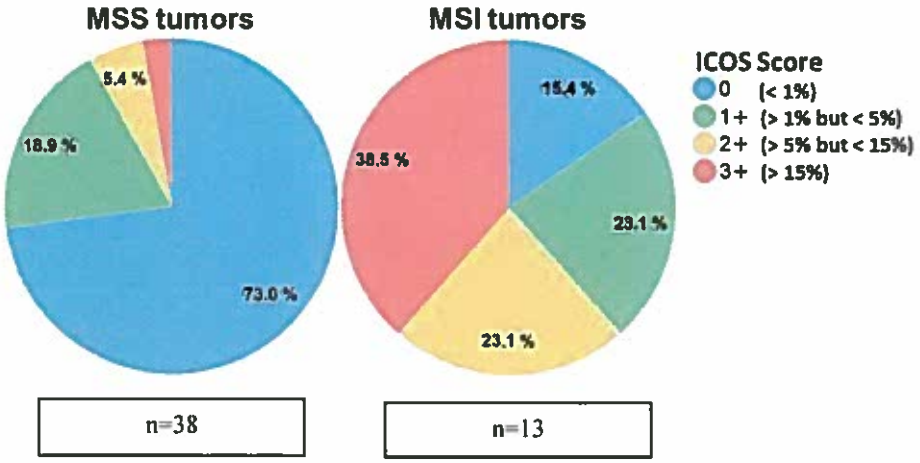
Further analysis conducted within Jounce Therapeutics has strengthened the rationale for exploration of JTX-2011 in gastric cancer. Gastric cancer as a whole exhibits an ICOS score of 2 or higher by IHC in approximately 28% of tumors tested. Exploration of ICOS expression within gastric cancer via an orthogonal RNAseq dataset (The Cancer Genome Atlas [TCGA] "STAD [stomach adenocarcinoma]"), indicates that the frequency of ICOS expression varies with respect to molecular subtype {Cancer Genome Atlas Research 2014} with the highest frequency of medium and high ICOS levels seen in microsatellite-instability high (MSI-H) and Epstein-Barr virus positive subsets. These subsets represent approximately 8-9.4% and 4-10%, respectively, of all gastric cancers {Boger 2016; Iizasa 2012; Kim 2016}, and are mutually exclusive.

MSI-H tumors in general are of particular interest, as mismatch repair deficiency is associated with a deficiency in the DNA repair pathways in a certain fraction of human tumors. These mismatch repair deficient, microsatellite instable (MSI) tumors accumulate 10-100 fold more mutations in the tumors as compared to the microsatellite stable counterparts {Cancer Genome Atlas Research 2014}. A MSI-H tumor may display more non-self or neo-antigens to the surrounding tumor microenvironment, and therefore be immunologically recognized as foreign. These non-self antigens may attract cells of the immune system such that they infiltrate the tumor. Thus as a consequence of a higher number of mutations, MSI-H tumors tend to have higher levels of infiltrate than those that are microsatellite stable (MSS) {Jass 1998}. MSI-H tumors, therefore, may be more likely to respond to immunotherapy {Le 2015}, as reflected by FDA approvals for nivolumab marketed as Opdivo in MSI-H colorectal cancer and Pembrolizumab, marketed as Keytruda® in MSI-H solid tumors regardless of tissue of origin (Opdivo® Full Prescribing Information{Bristol-Myers Squibb Company 2017a}, Keytruda® Full Prescribing Information{Merck & Co Inc 2017}).

Another example of an MSI-H tumor is endometrial cancers. Endometrial cancers also exhibit a population of MSI-H tumors that are known to be highly infiltrated. In a cohort of endometrial cancer patients, MSI status was determined by the presence or absence of mismatched repair genes (MLH1, MSH2, PMS2, MSH6) according to established guidelines {Egoavil 2013} at

Jounce. In order to understand whether ICOS was expressed in this population, ICOS IHC was performed in these endometrial tumor samples with known MSI status. Approximately 85% of MSI-H endometrial tumors have an ICOS score of at least 1 (Figure 4), whereas the MSS patients have low ICOS levels, making the MSI population very attractive for clinical exploration with JTX-2011. The recent FDA approval of pembrolizumab, marketed as Keytruda® {Merck & Co Inc 2017} in subjects with relapsed, unresectable or metastatic MSI-H solid tumors supports exploration of JTX-2011 in a broader population of MSI-H solid tumors beyond endometrial cancer.

Figure 4: ICOS IHC from endometrial cancer patient tumor samples



Abbreviations: MSI = microsatellite instability; MSS = microsatellite stable

PD-L1 expression in tumors has been associated with improved response to PD-1 inhibitors {Garon 2015; Topalian 2012}. Although ICOS expression is observed in PD-L1 positive tumors, up to 15% of PD-L1 negative tumors have high ICOS expression {JTX-2011 015}, suggesting a potential role for JTX-2011 in tumors that do not respond to PD-1 inhibitors.

JTX-2011 has several favorable safety related features. First, JTX-2011 does not indiscriminately cause polyclonal T cell activation but rather, immune stimulation through ICOS via JTX-2011 requires initial T cell priming {JTX-2011 003 and JTX-2011 012}, predicting that JTX-2011 will not have the toxicities of a superagonist. Second, nonclinical *in vitro* and *in vivo* studies suggest that JTX-2011 alone and in combination with nivolumab is not likely to induce toxic levels of inflammatory cytokines {JTX-2011 012}. Finally, the pharmacologic activity of JTX-2011 appears to be primarily focused within tumors, with minimal to no effect on T cells in peripheral blood, lymph nodes, or spleen, which may translate to fewer or less severe immune-related adverse events.

The safety profile of JTX-2011 in combination with nivolumab, pembrolizumab, or ipilimumab is expected to reflect the immunostimulatory effects of both molecules. Based on clinical data with nivolumab and pre-clinical data with JTX-2011 alone and in combination with nivolumab, the risk of acute inflammatory reactions due to cytokine induction is predicted to be low. Preclinical *in vitro* studies have been conducted to specifically look at cytokine release in

response to ipilimumab and JTX-2011 in combination, and data suggest that JTX-2011 alone or in combination with ipilimumab is not likely to induce toxic levels of inflammatory cytokines {JTX-2011 022}. Subjects treated with JTX-2011 alone and in combination will be monitored closely for immune-related adverse events, which are well described with nivolumab, ipilimumab and pembrolizumab therapy (both individually and in combination) and should be expected in combination with JTX-2011.

The IHC assay to be used for determining ICOS expression levels is analytically validated and run in a clinical central laboratory that meets the College of American Pathologist (CAP) & Clinical Laboratory Improvement Amendment (CLIA) guidelines. This assay is for investigational use only as it has not been approved by the FDA and, as such, the performance characteristics have not been established. ICOS score will be provided to clinical sites with a numerical value. For this protocol ICOS high is defined as a score of 2 or 3. ICOS low is defined as a score of 0 or 1.

Expected outcomes with standard therapy for these indications are presented in Table 2.

Table 2: Best outcomes with standard therapies

Indication	Best outcomes with standard therapies for recurrent or metastatic disease		
	First-line therapy	*Second-line therapy*	*Third-line therapy*
HNSCC	Erbitux + chemotherapy {Eli Lilly and Company 2016} • ORR 36% • PFS 6 mo. • OS 10 mo.	Opdivo {Bristol-Myers Squibb Company 2017a} • ORR 13% • OS 8 mo. Keytruda {Merck & Co Inc 2017} • ORR 16%	Unused first- and second-line therapies, depending on prior treatment and patient's resistance profile
NSCLC (non-EGFR, ALK, or ROS1 mutated)	Squamous or non-squamous: Chemotherapy ± Portrazza or Avastin {Eli Lilly and Company 2015; Genentech Inc. 2016; Patel 2013} ORR 33% • PFS 6 mo. • OS 12-13 mo. Keytruda (≥50% PD-L1+ only) {Merck & Co Inc 2017} • ORR 45% • PFS 10 mo. • OS >19 mo. Non-squamous: Keytruda + chemotherapy) {Merck & Co Inc 2017} • ORR 55% • PFS 13 mo. • OS >21 mo.	Squamous or non-squamous: Opdivo {Bristol-Myers Squibb Company 2017a} • ORR 27-56% • PFS 2-4 mo. • OS 9-12 mo. Keytruda (≥ 1% PD-L1+ only){Merck & Co Inc 2017} • ORR 18-19% • PFS 4 mo. • 10-13 mo. Tecentriq {Genentech, Inc. 2017} ORR 22% • OS 13 mo.	Unused first- and second-line therapies, depending on prior treatment and patient's resistance profile
TNBC (efficacy data for all breast cancer subtypes since data specific to TNBC data not available)	Combination chemotherapy{Hospira, Inc. 2014; Eli Lilly and Company 2014} • ORR 41-45% • OS 15-19 mo.	Chemotherapy{Bristol-Myers Squibb 2007; Genentech Inc. 2015} • ORR 12-26%	Chemotherapy{Eisai Inc. 2016} • OS 13 mo.
Melanoma (non-BRAF mutated)	Opdivo + Yervoy {Bristol-Myers Squibb Company 2017a; Bristol-Myers Squibb Company 2017b} • ORR 50% • PFS 11.5 mo.	Opdivo {Bristol-Myers Squibb Company 2017a} • ORR 34% • PFS 5 mo. • OS > 15 mo. Keytruda {Merck & Co Inc 2017} • ORR 33% • PFS 4 mo. • OS > 20 mo.	Unused first- and second-line therapies, depending on prior treatment and patient's resistance profile

Gastric cancer	Combination chemotherapy{Hospira, Inc. 2017; Luo 2011; MacDonald 1980} • ORR 37-44% • PFS 6-7 mo. • OS 6-11 mo.	Ramucirumab + chemotherapy {Eli Lilly and Company 2017} • ORR 28% • PFS 4.4 mo. • OS 9.6 mo. MSI-H: Pembrolizumab {Merck & Co Inc 2017} • ORR 56%.	Pembrolizumab (PD-L1+ only) {Merck & Co Inc 2017} • ORR 13%
Endometrial cancer	Combination chemotherapy {Miller 2012} • PFS 14 mo. • OS 32-38 mo.	Bevacizumab in combination with chemotherapy {Genentech Inc. 2016} • ORR 28% • PFS 6.8 mo. • OS 16.6 mo.	Unused first- and second-line therapies, depending on prior treatment and patient's resistance profile
Mesothelioma	Chemotherapy combinations with pemetrexed and/or cisplatin {Vogelzang 2003} • ORR 41.3% • PFS 5.7 mo. • OS 12.1 mo. Bevacizumab, pemetrexed and cisplatin for unresectable disease {Zalcman 2016} • PFS 9.2 mo. • OS 18.8 mo.	various experimental chemotherapy and IO regimens have demonstrated efficacy when used in second-line {NCCN 2017}, however, none are FDA approved	Unused first- and second-line therapies, depending on prior treatment and patient's resistance profile
Metastatic Castrate-Resistant Prostate cancer	Docetaxel+ Prednisone (if symptomatic) {Petrylak 2004; Tannock 2004} • OS 18.9 mo. Sipuleucel-T (if asymptomatic or minimally symptomatic) {El-Amm 2013} • OS 25.8 mo.	Cabazitaxel + prednisone {El-Amm 2013} • OS 15.1 mo. • PFS 2.8 mo. Abiraterone acetate + prednisone {El-Amm 2013} • OS 15.8 mo. • PFS 5.6 mo. Enzalutamide {El-Amm 2013} • OS 18.4 mo.	Unused first- and second-line therapies, other secondary hormone therapies depending on prior treatment, presence of visceral metastases and patient's resistance profile {NCCN 2017}

Abbreviations: ALK=anaplastic lymphoma kinase; EGFR=epidermal growth factor receptor; HNSCC=head and neck squamous cell carcinoma; MSI-H= microsatellite instability-high; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PFS=progression free survival.

1.4. Rationale for the Starting Dose and Schedule

1.4.1. Maximum Safe Starting Dose

Multiple approaches have been taken to compute the maximum safe starting dose using data from the monkey and rat toxicology studies, human PBMC cytokine release assays, minimum biologic effect dose in mice, a mechanistic PK model, and the minimum biologically active concentration (EC10) in the most relevant primary cell assay.

- JTX-2011 was well tolerated at doses up to 75mg/kg (the highest dose evaluated) in the pilot, repeat-dose monkey toxicity study, and 50mg/kg (the highest dose evaluated) in the GLP repeat-dose monkey study, and 15mg/kg (mid-dose) in the GLP rat toxicology

study. The NOAEL established in the GLP rat (15 mg/kg) and monkey (50 mg/kg) toxicology studies was used to compute a human equivalent dose (HED). HED doses are based on differences in predicted exposure and *in vitro* potency in the most relevant primary cell assay (primary CD4+ T cell assay) in each species. A 1000-fold safety factor was applied to the HED at NOAEL to reflect that JTX-2011 is an immune agonist and non-linear PK was observed in mice and rats. Taking a conservative approach and using the rat NOAEL of 15mg/kg, this maximum safe starting dose based on HED is 0.0038mg/kg.

- The minimum dose in the human *in vitro* cytokine release assay at which there was any change in cytokine levels compared with negative control was determined. Since no effect relative to a negative control mAb was observed up to the maximum concentration tested, the human dose that would produce a C_{max} concentration under this level was estimated. This dose is 4.0mg/kg.
- The minimum dose of JTX-1011-mG2a administered to mice for which there was any biological effect was determined. The most sensitive effect in mice was up-regulation of JTXP, a candidate biomarker, on B cells. The HED was then computed based on interspecies differences in exposure and potency. This dose is 0.0086mg/kg.
- The human dose was computed at which the projected C_{max} was less than the minimum biologically active concentration (EC10) in the most relevant primary cell assay (primary CD4+ T cell assay). This dose was 0.0044mg/kg.
- A mechanistic PK model was developed that accounts for linear and target-mediated clearance routes and predicts target engagement though binding to ICOS. Drug—ICOS binding is modeled using *in vitro* binding affinity (which is more potent than the EC_{50} in the primary T cell assay). This model was used to predict the dose that produces a maximum of 30% target engagement. Based on this model a 0.003mg/kg dose produced less than 30% TE at maximum.

The last method produced the most conservative and minimum safe starting dose based on all the types of calculations used. Based on this, a dose of 0.003mg/kg appears to be a reasonably safe starting dose.

1.4.2. JTX-2011 Schedule Determination

1.4.2.1. Rationale for Every 3 Week (q3w) Dosing

Pre-clinical PK and potency data supported up to a 3-week dosing interval. At the proposed highest dose of 1.0 mg/kg, sustained target engagement (greater than 95%) was predicted for the 3-week dosing interval.

Based on the preponderance of data, the proposed starting dose for Phase 1 is 0.003mg/kg and the proposed dose escalation schedule for the Phase 1, Part A is 0.003mg/kg, 0.01mg/kg, 0.03mg/kg, 0.1mg/kg, 0.3mg/kg, and 1mg/kg administered on a 21-day cycle.

1.4.2.2. Rationale for Every 6 Week (q6w) Dosing

The rationale for exploring JTX-2011 dosing q6w is based in part upon analysis of peripheral blood samples from a subset of subjects enrolled in Parts A, B, and C. While a small data set,

this analysis indicates that peripheral TE was saturated through the C2D1 time point (22 days). This potentially means that at the RP2D of JTX-2011 0.3 mg/kg q3w, there may be no peripheral target (ICOS) available for additional doses of JTX-2011 on which to bind. While single-agent activity has been observed at q3w in the form of stable disease, reductions of overall tumor burden, and an objective response, the analysis described above could suggest that without having available target for JTX-2011 to bind, additional drug administered at the q3w dosing interval may not provide added benefit in the monotherapy and combination settings. For this reason, we will explore the a q6w dosing schedule both in monotherapy and in combination. Additionally, as JTX-2011 will be dosed in combination with ipilimumab, pembrolizumab and potentially other combination partners, it is important to elucidate clinical activity and the safety profile of JTX-2011 at the q6w dosing schedule.

1.4.3. Starting Dose for JTX-2011 in Combination with Nivolumab

The starting dose for dose escalation of JTX-2011 in combination with nivolumab will be based on safety data from single-dose JTX-2011. If no dose limiting toxicity or other safety issues are observed through at least one cycle for the first three single-agent dose levels, combination with nivolumab is planned to start at the second dose level of JTX-2011. The RP2D for JTX-2011 in combination with nivolumab 240 mg q3w as determined from Part B is 0.3 mg/kg IV q3w.

1.4.4. Starting Dose for JTX-2011 in Combination with Ipilimumab

Based upon safety data with JTX-2011 monotherapy and JTX-2011 in combination with nivolumab, and in order to mitigate potential overlapping toxicity, JTX-2011 will be dosed at the q6w schedule. The starting dose of JTX-2011 for this combination is planned for 0.03 mg/kg, two dose levels below the RP2D.

1.4.5. Starting Dose for JTX-2011 in Combination with Pembrolizumab

The starting dose for JTX-2011 in combination with pembrolizumab is planned for 0.1 mg/kg at the q3w dosing schedule, which is one dose level below the RP2D of JTX-2011 in combination with, nivolumab, another PD-1 inhibitor, as determined during Part B of this trial.

Pending emerging safety and efficacy data from the Part B PK/PD expansion cohorts, Part D, and at the q3w dosing cohorts in Part H, the Sponsor may elect to explore dosing JTX-2011 at the q6w dosing schedule in combination with pembrolizumab.

1.5. Clinical Experience with JTX-2011

This is a first-in-human study with JTX-2011in combination with nivolumab, ipilimumab and pembrolizumab. Please refer to the most up to date Investigator's Brochure for clinical experience to date.

1.6. Adverse Events

1.6.1. JTX-2011 Monotherapy

Based on the preclinical toxicology and observations thus far in this trial, JTX-2011 does not appear to cause spontaneous activation of the immune system nor does it induce pro-inflammatory cytokines at levels likely to induce cytokine storm, so the risk of acute

inflammatory reactions due to cytokine induction is predicted to be low. However, JTX-2011 may cause signs and symptoms of an infusion reaction or cytokine storm which may include the following: headache, fever, facial flushing, pruritus, myalgia, nausea, chest tightness, dyspnea, vomiting, erythema, abdominal discomfort, diaphoresis, shivers, hypertension, hypotension, lightheadedness, palpitations, and urticaria.

Subjects will be observed for at least 1 hour after completion of JTX-2011 infusion for assessment of IV infusion tolerability.

JTX-2011 may be expected to cause adverse events similar to other immunotherapy agents, with immune-related toxicities caused by immune stimulation in organs not involved by cancer. As such, immune-related adverse events which can involve any organ system may be seen. These include pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, rash, and encephalitis (Opdivo® Full Prescribing Information {Bristol-Myers Squibb Company 2017a}.

1.6.2. JTX-2011 in Combination with Nivolumab

Based on clinical data with nivolumab and pre-clinical data with JTX-2011, the risk of acute inflammatory reactions due to cytokine induction is predicted to be low. Severe infusion reactions have been reported in < 1% of subjects in nivolumab clinical trials (Opdivo® Full Prescribing Information{Bristol-Myers Squibb Company 2017a; Michot 2016}). *In vitro* and *in vivo* studies with JTX-2011 do not predict a likelihood of cytokine storm. *In vitro* studies of cytokine induction with the combination of nivolumab and JTX-2011 in human PBMCs were performed, and no indication of cytokine storm was observed.

Subjects will be observed for at least 1 hour after completion of JTX-2011 and combination infusions for assessment of IV infusion tolerability.

Adverse events associated with administration of nivolumab may be increased in frequency or severity when combined with JTX-2011. These include pneumonitis, colitis, hepatobiliary disease including hepatitis, endocrinopathies, nephritis, rash, and encephalitis.

Subjects with liver metastasis, a history of hepatobiliary tract disease and evidence of significantly impaired liver function may not benefit from treatment with JTX-2011 and nivolumab.

1.6.3. JTX-2011 in Combination with Ipilimumab

Based on clinical data with ipilimumab, there is a risk of severe and potentially fatal acute immune-mediated adverse events due to T-cell activation and proliferation, which may involve any organ system. The most common reactions are: enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy and endocrinopathy (Yervoy® Full Prescribing Information{Bristol-Myers Squibb Company 2017b}). The majority of these immune-mediated reactions manifest during treatment. However, they may occur weeks to months after discontinuation of ipilimumab. Adverse events associated with administration of ipilimumab may be increased in frequency or severity when combined with JTX-2011.

In vitro studies of cytokine induction with the combination of ipilimumab and JTX-2011 in human PBMCs and whole blood were performed, and no indication of cytokine storm was observed {JTX-2011 022}.

1.6.4. JTX-2011 in Combination with Pembrolizumab

Based on clinical data with pembrolizumab, the risk of acute inflammatory reaction due to cytokine release is very low. Severe or life-threatening infusion-related reactions, including hypersensitivity and anaphylaxis, have been reported in 6 (0.2%) of 2799 patients treated with pembrolizumab. A risk of immune-mediated adverse reactions has occurred with clinical use of pembrolizumab, including (but not limited to): pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction and skin adverse reactions {Merck 2014}. No clinical or preclinical studies have been conducted to evaluate the safety of pembrolizumab in combination with JTX-2011. The mechanism of action and safety profile of pembrolizumab is very similar to that of nivolumab, which has been administered safely to subjects with advanced solid tumors in Study JTX-2011-101.

2. STUDY OBJECTIVES

2.1. Phase 1: Parts A, B, E, and G

2.1.1. Primary Objectives for Parts A, B, E, and G:

- Assess the safety and tolerability of JTX-2011 monotherapy (Part A), JTX-2011 in combination with nivolumab (Part B), JTX-2011 in combination with ipilimumab (Part E), and JTX-2011 in combination with pembrolizumab (Part G) in subjects with advanced and/or refractory solid tumor malignancies after single and multiple ascending doses;
- Determine the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D) of JTX-2011 (Part A), JTX-2011 in combination with nivolumab (Part B), JTX-2011 in combination with ipilimumab (Part E), and JTX-2011 in combination with pembrolizumab (Part G) in subjects with advanced and/or refractory solid tumor malignancies.

2.1.2. Secondary Objectives for Parts A, B, E, and G:

- Assess the pharmacokinetics (PK) and pharmacodynamics (PD) of single and multiple ascending doses of JTX-2011 when administered as monotherapy (Part A), JTX-2011 in combination with nivolumab (Part B), JTX-2011 in combination with ipilimumab (Part E), and JTX-2011 in combination with pembrolizumab (Part G);
- Assess the pharmacokinetics (PK) of nivolumab when administered in combination with JTX-2011 (Part B);
- Assess the pharmacokinetics (PK) of ipilimumab when administered in combination with JTX-2011 (Part E);
- Assess the pharmacokinetics (PK) of pembrolizumab when administered in combination with JTX-2011 (Part G).

2.1.3. Exploratory Objectives for Parts A, B, E, and G:

- Evaluate the effect of JTX-2011 monotherapy (Part A), JTX-2011 in combination with nivolumab (Part B), JTX-2011 in combination with ipilimumab (Part E) and JTX-2011 in combination with pembrolizumab (Part G) on peripheral blood immune cell markers and gene signatures;
- Evaluate efficacy (response rate, duration of response, disease control rate, landmark progression free survival rate, progression free survival, landmark overall survival rate, and overall survival) of JTX-2011 as monotherapy (Part A), JTX-2011 in combination with nivolumab (Part B), JTX-2011 in combination with ipilimumab (Part E), and JTX-2011 in combination with pembrolizumab (Part G) in subjects with advanced and/or refractory solid tumor malignancies;
- Examine the correlation between potential predictive biomarkers of response and efficacy (response rate, duration of response, disease control rate, landmark progression free survival rate, progression free survival; landmark overall survival rate, and overall survival);
- Examine changes from baseline in gene signatures and immune cell subsets within tumor biopsies after treatment with either JTX-2011 monotherapy or a combination of JTX-2011 with nivolumab (Safety/PK/PD Expansion Cohorts AP1, AP2, BP1, BP2).

2.2. Objectives for Phase 2: Parts C, D, F, and H

2.2.1. Primary Objectives for Parts C, D, F, and H:

- Evaluate preliminary efficacy (response rate, duration of response, disease control rate, landmark progression free survival rate, progression free survival, landmark overall survival rate, and overall survival) of JTX-2011 monotherapy (Part C), JTX-2011 in combination with nivolumab (Part D), JTX-2011 in combination with ipilimumab (Part F), and JTX-2011 in combination with pembrolizumab (Part H) in subjects with specific advanced and/or refractory solid tumor malignancies;

- Part C: Confirm the safety and tolerability of JTX-2011 monotherapy in eight (8) indication-specific groups, each with stratification for ICOS expression based upon the fresh tissue biopsy: C01- head and neck squamous cell carcinoma [HNSCC, dosed q3w]; C02 - non-small cell lung cancer [NSCLC, dosed q3w]; C03 - advanced refractory solid tumors other than those eligible for C01, C02, C04, or C05 (dosed q3w) (*closed to enrollment*); C04 - gastric cancer or gastroesophageal junction adenocarcinoma (dosed q3w); C05 - MSI-H or dMMR endometrial cancer (*closed to enrollment*); C06 - triple negative breast cancer [TNBC, dosed q3w]; C07 – mesothelioma (dosed q3w); and C64 – gastric cancer or gastroesophageal junction adenocarcinoma (dosed q6w);
- Part D: Confirm the safety and tolerability of JTX-2011 (dosed q3w) in combination with nivolumab therapy in six (6) indication-specific expansion groups, including 5 with stratification for ICOS expression: D01 - HNSCC; D02 - NSCLC; D03 - TNBC; D04 - melanoma (*closed to enrollment*); D05 - gastric cancer; and 1 group without stratification: D06 - MSI-H or dMMR endometrial cancer (*closed to enrollment*);
- Part F: Confirm the safety and tolerability of JTX-2011 in combination with ipilimumab (dosed q6w) therapy in two (2) indication-specific groups, neither with stratification for ICOS expression: F61 - metastatic castrate-resistant prostate cancer [mCRPC, dosed q6w]; and F62 – melanoma (dosed q6w);
- Part H: Confirm the safety and tolerability of JTX-2011 in combination with pembrolizumab therapy in six (6) indication or biomarker-specific groups, each with stratification for ICOS expression based upon the fresh biopsy: H31 – HNSCC (dosed q3w); H32 – NSCLC (dosed q3w); H33 – TNBC (dosed q3w); H34 – gastric cancer or gastroesophageal junction adenocarcinoma (dosed q3w); H35 – MSI-H solid tumors (dosed q3w); H64 – gastric cancer or gastroesophageal junction adenocarcinoma (dosed q6w);
- Confirm the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D) of JTX-2011 monotherapy (Part C), JTX-2011 in combination with nivolumab (Part D), JTX-2011 in combination with ipilimumab (Part F), and JTX-2011 in combination with pembrolizumab (Part H).

2.2.2. Secondary Objectives for Parts C, D, F, and H:

- Confirm the pharmacokinetics (PK) and pharmacodynamics (PD) of JTX-2011 when administered as monotherapy (Part C), JTX-2011 in combination with nivolumab (Part D), JTX-2011 in combination with ipilimumab (Part F), and JTX-2011 in combination with pembrolizumab (Part H);

- Confirm the pharmacokinetics (PK) of nivolumab when administered in combination with JTX-2011 (Part D);
- Confirm the pharmacokinetics (PK) of ipilimumab when administered in combination with JTX-2011 (Part F);
- Confirm the pharmacokinetics (PK) of pembrolizumab when administered in combination with JTX-2011 (Part H).

2.2.3. Exploratory Objectives for Parts C, D, F, and H:

- Examine the correlation between potential predictive biomarkers of response and efficacy (response rate, duration of response, disease control rate, landmark progression free survival rate, progression free survival, landmark overall survival rate, and overall survival);
- Evaluate the effect of JTX-2011 monotherapy (Part C), JTX-2011 in combination with nivolumab (Part D), JTX-2011 in combination with ipilimumab (Part F) and JTX-2011 in combination with pembrolizumab (Part H) on peripheral blood immune cell markers and gene signatures;
- Examine changes from baseline in gene signatures and immune cell subsets within tumor biopsies after treatment with JTX-2011 monotherapy (Part C) and JTX-2011 in combination with ipilimumab (Part F).

3. INVESTIGATIONAL PRODUCT INFORMATION AND PROCUREMENT

3.1. Investigational Product Information

JTX-2011 is a humanized IgG1κ agonist monoclonal antibody, manufactured in CHO cells and supplied as a liquid vial for injection: 20mg/vial in 20mM L-histidine, 60mM sucrose, 60mM mannitol, pH 6.0 with Polysorbate 80 at 0.01% (w/v).

Compound Name: JTX-2011

Formulation: JTX-2011 (20mg) is supplied in a single-use Type 1 glass vial as a 10mg/mL solution containing L-Histidine (USP), L-Histidine Monohydrochloride (FCC, BP, EP), Sucrose (USP/NF, EP, JP), Mannitol (USP, EP, JP), and Polysorbate 80 (NF, EP, JP). JTX-2011 does not contain animal or animal-derived components.

JTX-2011 has been tested to be soluble when diluted in 0.9% Sodium Chloride for injection (USP) at the envisioned clinical dose range.

Storage Requirements: JTX-2011 vials are stored at 2–8°C (36–46°F) until ready for use. JTX-2011 vials should be protected from light. Do not freeze or shake. JTX-2011 solutions diluted in Normal Saline (0.9% Sodium Chloride for Injection, USP) may be stored at Controlled Room Temperature 20-25°C (68-77°F) for up to 6 hours. JTX-2011 is **not** compatible with Dextrose.

For more information please refer to the Pharmacy Manual.

3.2. JTX-2011 Dosage and Administration

JTX-2011 is administered as a single agent and in combination with nivolumab at a 0.3mg/kg dose as a 1-hour IV infusion (-5/+10 minutes) every 3 or 6 weeks. The dose of JTX-2011 in combination with ipilimumab and pembrolizumab will be determined in this study.

Standard institutional procedures for accessing and assessing intravenous catheters should be followed with each infusion. Please refer to the Pharmacy Manual for more information.

In parts of the study in which JTX-2011 is administered on the same day as nivolumab, ipilimumab, or pembrolizumab, JTX-2011 should be dosed first with a 30-minute (-5/+10 minutes) evaluation period prior to administration of combination therapy. In instances where an infusion reaction occurs during dosing of JTX-2011, administration of combination therapy may be delayed beyond the 30-minute (-5/+10 minutes) evaluation period.

3.3. Nivolumab Dosage and Administration

Nivolumab, marketed as Opdivo®, is a human IgG4κ anti-PD-1 monoclonal antibody manufactured by Bristol-Myers Squibb for the treatment of cancer. Nivolumab acts as an immunomodulator by blocking ligand activation of the programmed cell death 1 (PD-1) receptor on activated T cells.

3.3.1. Nivolumab Dosing Part C

For subjects in Part C who elect to add nivolumab post confirmed disease progression (Section 5.5), nivolumab will be administered as a one-hour IV infusion (-5/+10 minutes), 240mg IV q3w. Please refer to the Pharmacy Manual for more information. 5.5.1).

3.3.2. Nivolumab Dosing Parts B and D

For subjects enrolled to Parts B and D, nivolumab will be administered as a one-hour IV infusion (-5/+10 minutes), 240 mg IV q3w to coincide with JTX-2011 q3w dosing. Please refer to the Pharmacy Manual for more information.

3.4. Ipilimumab Dosage and Administration

Ipilimumab, marketed as Yervoy®, is a human IgG1κ cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody manufactured by Bristol-Myers Squibb for the treatment of melanoma. Ipilimumab binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Ipilimumab, in this study, will be administered as a 90-minute IV infusion (-5/+10 minutes), 3 mg/kg q3w for a total of four doses. Please refer to the Pharmacy Manual and the Yervoy® Full Prescribing Information{Bristol-Myers Squibb Company 2017b} for more information.

3.5. Pembrolizumab Dosage and Administration

Pembrolizumab, marketed as Keytruda®, is a humanized IgG4 anti-PD-1 monoclonal antibody manufactured by Merck for the treatment of cancer. Pembrolizumab acts as an immunomodulator by blocking ligand activation of the programmed cell death 1 (PD-1) receptor on activated T cells. Pembrolizumab, in this study, will be administered as a 30-minute IV infusion (-5/+10 minutes), 200 mg IV q3w. Please refer to the Pharmacy Manual for more information.

3.6. Study Drug

Study drug is hereby defined as JTX-2011 monotherapy and JTX-2011 in combination with nivolumab, ipilimumab, or pembrolizumab.

3.7. Study Drug Procurement

3.7.1. Drug Ordering

The initial shipment of study drug (e.g. JTX-2011, nivolumab, pembrolizumab, and ipilimumab) to a clinical site will occur after all essential regulatory documents are collected for that site. Please refer to the Pharmacy Manual for information on re-supply shipments.

3.7.2. Drug Accountability

Each Investigator/designee is responsible for taking an inventory of each shipment of study drug supplied by the Sponsor received and comparing it with the accompanying accountability form.

JTX-2011, nivolumab, pembrolizumab, and ipilimumab must be used only as directed in this protocol. The Investigator/designee must keep accurate written records of all study drug received

from Jounce/Sponsor Representative. Additionally, the Investigator/designee must keep accurate records of JTX-2011, nivolumab, pembrolizumab, and ipilimumab dispensed to subjects in this protocol including the number of vials used to prepare subject doses, lot number, date dispensed, subject identification number, dose administered, balance forward, and the initials of the person dispensing the medication. Based on the entries in the site drug accountability forms, it must be possible to reconcile drug product delivered with that used. All study drug must be accounted for and all discrepancies investigated and documented appropriately.

JTX-2011, nivolumab, pembrolizumab, and ipilimumab stock may not be removed from the investigative site where originally shipped without prior knowledge and consent of Jounce or their delegated CRO.

At the end of the study, all unused vials of JTX-2011, nivolumab, pembrolizumab, and ipilimumab will be destroyed by the investigative site according to that site's drug destruction procedures. All certificates of delivery/drug receipts must be signed prior to shipment.

3.8. Contraindications

Based on the immune-stimulatory mechanism of action of JTX-2011, it should not be administered to subjects with any of the following:

- History of intolerance, hypersensitivity, formation of anti-drug antibodies, or severe immune-related adverse events to prior immunotherapies, including CTLA-4 inhibitors, PD-1 inhibitors, or immune agonists. Subjects who discontinued prior immunotherapies for immune-related adverse events that are well-controlled with appropriate treatment, and, in the opinion of the investigator, should not prevent the subject from receiving study drug, may be enrolled if approved by the medical monitor;
- Active disease requiring systemic immunosuppressive therapy;
- Any known primary or acquired diagnosis of immunodeficiency, or treatment with systemic steroids or any other form of immunosuppressive therapy within 7 days prior to C1D1. Exception: inhaled or topical steroids and adrenal replacement doses are permitted in the absence of active autoimmune disease;
- Known severe intolerance to or life-threatening hypersensitivity reactions to humanized monoclonal antibodies or intravenous immunoglobulin preparations; any history of anaphylaxis; prior history of human anti-human antibody response; known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent.

3.8.1. Concomitant Medications

Documentation of concomitant medication use will be recorded at each visit.

3.8.1.1. Prohibited Concomitant Medications/Therapies

Immune-suppressive steroids or any other form of immunosuppressive therapy within 7 days prior to C1D1

3.8.1.2. Allowed Concomitant Medications

- Inhaled, topical or oral steroids and adrenal replacement doses are permitted.

- Palliative radiation to non-target lesions only is allowed during study treatment in consultation with the medical monitor.
- One-time dose of immunosuppressive agents used prophylactically for contrast allergies

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

All subjects must meet the following inclusion criteria to be eligible for study participation:

1) Must be willing and able to participate and comply with all trial requirements and able to provide signed and dated informed consent prior to initiation of any trial procedures;
2) **All Parts:**
   a) Evaluable or measurable disease, according to RECIST v1.1 criteria, with at least one measurable lesion (except for Parts A, B, E and G, see below);
   b) Meets the requirements for the intended study cohort.
3) **Parts A, B and E Dose Escalation:**
   Any advanced and/or refractory, non-hematological, extracranial malignancy with disease progression after treatment with all available therapies known to confer clinical benefit. Subjects enrolled to dose escalation cohorts may have evaluable but non-measurable disease.
4) **Parts A and B Safety/PK/PD Expansion Cohorts (AP1, AP2, BP1, and BP2):**
   a) Any advanced and/or refractory, non-hematological, extracranial malignancy with disease progression after treatment with all available therapies known to confer clinical benefit, with ≥ 1 ICOS expression levels as determined by immunohistochemistry on archival tumor or history of documented PD-L1 expression;
   b) Must have a tumor lesion that can be biopsied at acceptable risk and must agree to both a fresh biopsy between screening and C1D1 and a second biopsy after completion of 2 cycles of study treatment.
5) **Part C –** all subjects must have progressed on or after all approved therapies. If prior therapy included a PD-1 inhibitor, subjects must have progressed after at least 2 months of this therapy:
   a) C01: HNSCC;
   b) C02: NSCLC;
   c) C03: Any advanced, non-hematological, extracranial malignancy other than those eligible for C01, C02, C04, or C05 *(closed to enrollment)*;
   d) C04 and C64: Gastric or gastroesophageal junction adenocarcinoma, including adenocarcinoma of the lower esophagus. Subjects with HER2 over-expressing tumors must have progressed on or after FDA approved therapy for HER2 over-expressing metastatic gastric or gastroesophageal junction adenocarcinoma;
   e) C05: Endometrial cancer that is locally determined to have a mismatch repair deficiency (dMMR) as determined by immunohistochemical complete loss of expression (absence of nuclear immunoreactivity) of at least one of the mismatch repair genes MSH2, MSH6, MLH1 and PMS2, or to be microsatellite instability-high (MSI-H) by polymerase chain reaction (PCR) *(closed to enrollment)*;

f) C06: TNBC that is immunotherapy naïve [negative per ASCO/CAP guidelines for estrogen receptor (ER) protein expression and progesterone receptor (PR) protein expression (< 1% of tumor cell nuclei are immunoreactive), and negative for human epidermal growth factor receptor (HER2) protein expression by IHC assay (0 or 1) or by fluorescence *in situ* hybridization (FISH)];
g) C07: Mesothelioma that is immunotherapy naïve;

6) **Part D:**

a) D01: HNSCC that progressed on or after at least 2 months of a prior PD-1 inhibitor;
b) D02: NSCLC that progressed on or after at least 2 months of a prior PD-1 inhibitor; Subjects with EGFR or ALK genomic tumor aberrations must have progressed on or after FDA approved therapy for these aberrations;
c) D03: TNBC [negative per ASCO/CAP guidelines for estrogen receptor (ER) protein expression and progesterone receptor (PR) protein expression (< 1% of tumor cell nuclei are immunoreactive), and negative for HER2 protein expression by IHC assay (0 or 1+) or by FISH];
d) D04: Melanoma that progressed on or after at least 2 months of a prior PD-1 inhibitor *(closed to enrollment)*;
e) D05: gastric cancer, including subjects with cancer of the gastro-esophageal (G-E) junction. Subjects with HER2 over-expressing tumors must have progressed on or after FDA approved therapy for HER2 over-expressing metastatic gastric or gastroesophageal junction adenocarcinoma;
f) D06: Endometrial cancer that is locally determined to have a dMMR as determined by IHC complete loss of expression (absence of nuclear immunoreactivity) of at least 1 of the mismatch repair genes MSH2, MSH6, MLH1 and PMS2, or to be MSI-H by PCR *(closed to enrollment)*;
g) If a PD-1 or PD-L1 inhibitor is approved for treatment of TNBC during enrollment of this study, eligibility for subjects within that indication will require progression during or after prior treatment with the approved PD-1 or PD-L1 inhibitor;

7) **Part F:**

a) F61: mCRPC that has progressed on or after treatment with at least 1 prior standard of care therapy;
b) F62: Unresectable or metastatic melanoma with ≤ 2 prior lines of therapy in the unresectable or metastatic setting;

8) **Part G:**

a) Recurrent or metastatic HNSCC previously treated with with disease progression on or after platinum-containing chemotherapy;

b) Metastatic NSCLC that has high PD-L1 expression (TPS ≥ 50%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations;

c) Recurrent or metastatic gastric or gastroesophageal junction adenocarcinoma or adenocarcinoma of the lower esophagus with disease progression on or after one prior line of therapy, including HER2/neu-targeted therapy, if appropriate;

d) Recurrent or metastatic MSI-H solid tumors that have progressed on prior FDA-approved treatment and who have no satisfactory alternative treatment options or MSI-H colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin and irinotecan;

e) Any advanced and/or refractory, non-hematological, extracranial malignancy with disease progression after treatment with all available therapies known to confer clinical benefit.

9) **Part H** – all subjects must be immunotherapy naive:

a) H31: Recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy;
b) H32: Metastatic NSCLC that has high PD-L1 expression (TPS ≥ 50%), as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations;
c) H33: metastatic or recurrent TNBC [negative per ASCO/CAP guidelines for ER protein expression and PR protein expression (< 1% of tumor cell nuclei are immunoreactive), and negative for HER2 protein expression by IHC assay (0 or 1) or by FISH] with ≤ 1 prior line of therapy in the metastatic or recurrent setting;
d) H34 and H64: Recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma including adenocarcinoma of the lower esophagus with disease progression on or after 1 prior line of therapy, including HER2/neu-targeted therapy, if appropriate;
e) H35: Unresectable or metastatic MSI-H solid tumors that have progressed on prior FDA-approved treatment and who have no satisfactory alternative treatment options or MSI-H colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan;

10) Male or Female ≥ 18 years of age;
11) Have an ECOG performance status 0-1. Subjects with ECOG 2 may be considered for enrollment in Parts C, D, F and H if approved by medical monitor;
12) Have a predicted life expectancy of ≥ 3 months;
13) Have the following laboratory values:

a) Serum creatinine < 2 × ULN
b) Total bilirubin ≤ ULN unless prior history of Gilbert's syndrome;
c) Aspartate transaminase and alanine transaminase ≤ 2.5 × ULN;
d) Hemoglobin ≥ 9.0 g/dL;
e) Platelets ≥ 75×10^9 cells/L;

f) Absolute neutrophil count ≥ 1.5 $\times 10^9$ cells/L (without the use of hematopoietic growth factors). Subjects with lower ANC may be enrolled if not the result of prior therapy, if approved by medical monitor;
g) Serum albumin ≥ 75% of LLN;

14) If medical history of the following, case should be reviewed with the Medical Monitor:
a) Prior biliary tract disorders (as based on Hepatobiliary SOC high level terms of: obstructive bile duct disorders, hepatic vascular disorders, structural and other bile duct disorders)
b) Portal hypertension and/or hepatic vascular disorders
15) Women of child-bearing potential (WOCBP) must have a negative serum pregnancy test at screening and a negative urine pregnancy test prior to administration of each dose of JTX-2011;
16) WOCBP and males with partners of child-bearing potential must agree to use adequate birth control throughout their participation and for 5 months following the last study treatment.

4.2. Exclusion Criteria

A subject with any one of the following criteria will not be eligible for study participation:

1) Receiving concurrent anti-cancer treatment (excluding radiation therapy, either approved or investigational; please see Section 3.8.1.1);
2) Have refused standard therapy;
3) Have received anti-cancer therapies listed below within the specified timeframe, or who have ongoing toxicity from prior therapy > Grade 1 according to the Common Terminology for Adverse Events (CTCAE). Exceptions to this are: > Grade 1 toxicities which in the opinion of the Investigator should not exclude the patient (e.g. alopecia, Grade 2 neuropathy, hypo- or hyperthyroidism or other endocrinopathies that are well-controlled with hormone replacement) and are approved by the Medical Monitor.

a) Have received biologic therapy, including immunotherapy, < 28 days prior to C1D1;
b) Have received a CAR-T therapy;
c) Have received chemotherapy < 21 days prior to C1D1, or < 42 days for mitomycin or nitrosoureas;
d) Have received targeted small molecule therapy < 14 days prior to C1D1;
e) Have undergone organ transplantation including allogeneic or autologous stem-cell transplantation, at any time;

4) Have undergone a major surgery (excluding minor procedures, e.g. placement of vascular access, biopsy, etc.) < 6 weeks prior to the first day of study treatment, C1D1;

5) Have a history of intolerance, hypersensitivity, or treatment discontinuation due to severe immune adverse events on prior immunotherapy, or documented presence of neutralizing anti-drug antibody to nivolumab (Parts B and D), ipilimumab (Part E and F), or pembrolizumab (Parts G and H). Subjects who discontinued prior immunotherapies for immune-related adverse events that are well-controlled with appropriate treatment may be enrolled if approved by the Medical Monitor;
6) Have a diagnosis of immunodeficiency, either primary or acquired, or treatment with systemic steroids or any other form of immunosuppressive therapy within 7 days prior to C1D1. Exception: inhaled or topical steroids and adrenal replacement doses are permitted in the absence of active autoimmune disease as well as a one-time dose of immunosuppressive agents used prophylactically for contrast allergies;
7) Have any active disease requiring systemic immunosuppressive treatment;
8) Have known severe intolerance to or life-threatening hypersensitivity reactions to humanized monoclonal antibodies or intravenous immunoglobulin preparations; any history of anaphylaxis; prior history of human anti-human antibody response; known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent;
9) Are symptomatic or have uncontrolled brain metastases, leptomeningeal disease, or spinal cord compression not definitively treated with surgery or radiation (brain metastases that are stable and asymptomatic, either treated or untreated, will be allowed);
10) Have current second malignancy at other sites, which requires treatment, or in the judgement of the Investigator, may require treatment within the next year. Concurrent malignancies that do not require treatment and are clinically stable are allowed. A past history of other malignancies is allowed as long as the subject is not receiving specific treatment other than hormonal therapy, and, in the judgement of the Investigator, is unlikely to have a recurrence;
11) Have active and clinically relevant bacterial, fungal, or viral infection, including known Hepatitis A, B, or C or HIV (testing not required);
12) Have received live vaccines within past 30 days (inactivated vaccines are allowed; seasonal vaccines should be up to date prior to first infusion day);
13) Women who are pregnant or breastfeeding;
14) Have experienced symptomatic cardiac disease that is unresponsive to surgical or medical management;
15) Have any medical or social condition that, in the opinion of the Investigator, might place a subject at increased risk, affect compliance, or confound safety or other clinical trial data interpretation.

4.3. Reproductive Restrictions

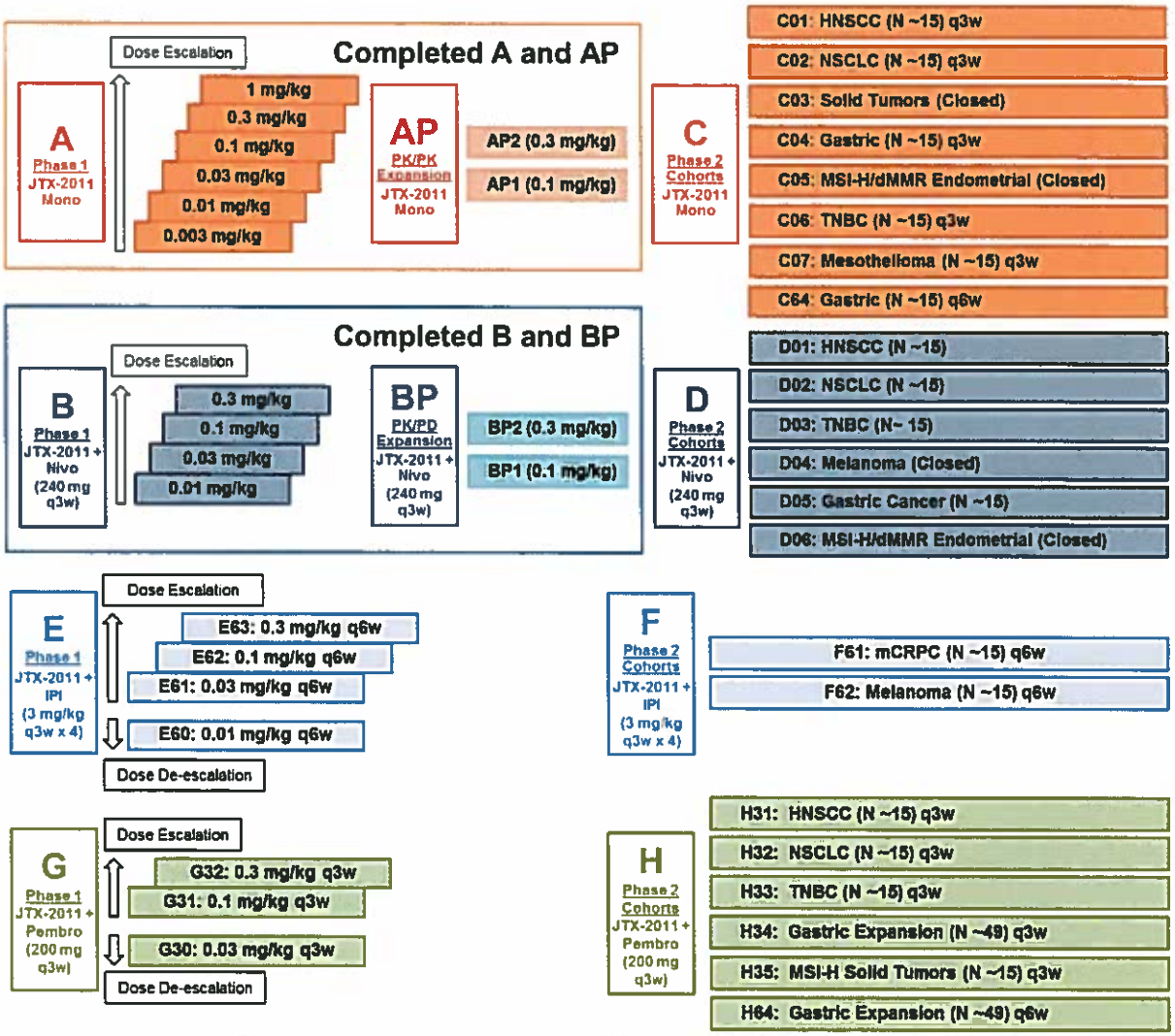
There are no data regarding the effect of JTX-2011 on the unborn fetus. JTX-2011 should not be administered to pregnant women. Embryo-fetal toxicity is a labeled warning for nivolumab, ipilimumab, and pembrolizumab (Opdivo® Full Prescribing Information{Bristol-Myers Squibb Company 2017a}, Yervoy® Full Prescribing Information{Bristol-Myers Squibb Company

2017b}, Keytruda® Full Prescribing Information{Merck & Co Inc 2017}). Women of child-bearing potential (WOCBP) must have a negative serum pregnancy test during screening period and a negative urine pregnancy test prior to administration of each dose of JTX-2011 throughout the study. Women of childbearing potential and males with partners of child-bearing potential must agree to use adequate birth control throughout their participation and for 5 months following the last study treatment.

5. STUDY DESIGN

This is a Phase 1/2, open label, multicenter, first-in-human trial to evaluate the safety and tolerability, PK, pharmacodynamics, and preliminary efficacy of the ICOS agonist monoclonal antibody JTX-2011 alone and in combination with nivolumab, ipilimumab, or pembrolizumab in adult subjects with advanced and/or refractory solid tumor malignancies. The study will be conducted at approximately 36 sites in North America. The study is divided into 8 parts; Part A, Part B, Part C, Part D, Part E, Part F, Part G, and Part H. Subjects may be enrolled into any open cohorts for which they qualify at the discretion of the Investigator.

Figure 5: JTX-2011-101 Study Schema



Abbreviations: dMMR=mismatch repair deficient; HNSCC=head and neck squamous cell carcinoma; PK=pharmacokinetics; PD=pharmacodynamics; mCRPC=metastatic castration-resistant prostate cancer; MSI-H= microsatellite instability-high; NSCLC=non-small cell lung cancer; TNBC=triple-negative breast cancer.

Approximately 498 evaluable subjects will be enrolled, assuming the following:

5.1. Part A (JTX-2011 Monotherapy Dose Escalation) – Completed Enrollment

Part A comprises escalating doses of JTX-2011 administered intravenously (IV) once every 3 weeks in consecutive cohorts, plus Safety/PK/PD Expansion Cohorts (AP1 and AP2) at each of two or more dose levels. A total of 27 subjects were enrolled across six (6) dose levels. An additional 12 subjects were enrolled in the safety and PK/PD data (Safety/PK/PD Expansion Cohorts AP1 and AP2). Archival tumor tissue will be collected on all dose escalation subjects for retrospective assessment of ICOS and PD-L1 expression. Subjects enrolled in AP1 and AP2 will be required to have ≥ 1 ICOS expression levels as determined by IHC on archival tumor tissue or history of documented PD-L1 expression as well as fresh tumor biopsies prior to C1D1 and after two cycles of study treatment for assessment of potential predictive biomarkers and to assess changes in T cell subsets and gene expression after treatment with JTX-2011. A minimal level of ICOS or PD-L1 expression implies the presence of T cells in the tumor, which is required for evaluation of changes in T cell subsets after treatment.

5.2. Part B (JTX-2011 in Combination with Nivolumab Dose Escalation) – Completed Enrollment

Part B comprises escalating doses of JTX-2011 in combination with nivolumab (both agents administered IV once every 3 weeks) in consecutive cohorts, plus Safety/PK/PD Expansion Cohorts (BP1 and BP2) at each of two or more dose levels. A total of 16 subjects were enrolled across four (4) dose levels. An additional 15 subjects were enrolled in the safety and PK/PD data (Safety/PK/PD Expansion Cohorts BP1 and BP2). Archival tumor tissue will be collected on all dose escalation subjects for retrospective assessment of ICOS and PD-L1 expression. Subjects enrolled in BP1 and BP2 will be required to have ≥ 1 ICOS expression levels as determined by IHC on archival tumor tissue or history of documented PD-L1 expression as well as fresh tumor biopsies prior to C1D1 and after two cycles of study treatment for assessment of potential predictive biomarkers and to assess changes in T cell subsets and gene expression after treatment with JTX-2011. A minimal level of ICOS or PD-L1 expression implies the presence of T cells in the tumor, which are required for evaluation of changes in T cell subsets after treatment.

5.3. Part E (JTX-2011 in Combination with Ipilimumab Dose Escalation)

Part E comprises escalating doses of JTX-2011 in combination with ipilimumab in consecutive cohorts (JTX-2011 will be administered IV q6w and will be administered until a subject meets criteria for discontinuation; ipilimumab will be administered IV q3w for up to 4 doses).

Three (3) dose escalation cohorts are planned at doses of 0.03 mg/kg, 0.1 mg/kg, and 0.3 mg/kg (approximately 3 dose levels with a minimum of 3 or up to 6 subjects per dose level, exclusive of replacement subjects and evaluation of escalation dose levels [approximately 18 subjects]). A dose de-escalation cohort of 0.01 mg/kg of JTX-2011 may be explored.

Table 3: Part E Dose Escalation Schema

Cohort	JTX-2011 Dose
E63	0.3 mg/kg
E62	0.1 mg/kg
E61*	0.03 mg/kg
E60	0.01 mg/kg

* Starting dose level

5.4. Part G (JTX-2011 in Combination with Pembrolizumab Combination Dose Escalation)

Part G comprises JTX-2011 in combination with pembrolizumab in consecutive cohorts (both agents administered IV q3w until a subject meets criteria for discontinuation).

Two (2) dose escalation cohorts are planned at doses of 0.1 mg/kg and 0.3 mg/kg (approximately 2 dose levels with a minimum of 3 or up to 6 subjects per dose level, exclusive of replacement subjects and evaluation of escalation dose levels [approximately 12 subjects]). A dose de-escalation cohort of 0.03 mg/kg of JTX-2011 may be explored.

Subjects in Part G are required to have a fresh tumor biopsy during screening. In situations where archival tissue is not available or biopsies are not feasible (e.g., would expose the subject to unreasonable health risks), one or more of these requirements may be waived after discussion with the Medical Monitor.

Table 4: Part G Dose Escalation Schema

Cohort	JTX-2011 Dose
G32	0.3 mg/kg
G31*	0.1 mg/kg
G30	0.03 mg/kg

* Starting dose level

5.5. Part C (JTX-2011 Monotherapy Phase 2)

Part C will include approximately 15 subjects in each of 8 dose cohorts (total of 120 subjects) in the indications listed below at 0.3 mg/kg in both the q3w and q6w dosing schedule. All subjects must have progressed on or after all approved therapies. If prior therapy included a PD-1 inhibitor, subjects must have progressed after at least 2 months of this therapy:

<u>q3w JTX-2011 dosing</u>

- C01: HNSCC;
- C02: NSCLC;
- C03: Any tumor type other than those eligible for C01, C02, C04, or C05 (*closed to enrollment*);
- C04: Gastric cancer or gastroesophageal junction adenocarcinoma;
- C05: MSI-H or dMMR endometrial cancer (*closed to enrollment*);

- C06: TNBC that is immunotherapy naïve;
- C07: Mesothelioma that is immunotherapy naïve.

q6w JTX-2011 dosing

- C64: Gastric cancer or gastroesophageal junction adenocarcinoma

Pre-screening for ICOS will not be required. Subjects in Part C are required to have archival tumor and two fresh tumor biopsies (one during screening and one post-dose between C2D1 and C3D1 for subjects on the q3w, or between C2D1 and C2D22 for subjects on the q6w). In situations where archival tissue is not available or biopsies are not feasible (e.g., would expose the subject to unreasonable health risks), one or more of these requirements may be waived after discussion with the Medical Monitor.

To complete enrollment in the HNSCC (C01), NSCLC (C02), gastric (C04 and C64), and TNBC (C06), at least 15 assessable pre-treatment fresh biopsies must have been obtained in each cohort, 10 of which must have an ICOS score ≥2. To complete enrollment in the mesothelioma cohort (C07), 10 subjects must have enrolled with ICOS ≥ 2 based on archival tissue, rather than fresh tissue.

If a subject has progressed in Part C, nivolumab can be added to the subject's treatment regimen after confirmation of progression and at the discretion of the Sponsor and investigator. After the completion of Part G, instead of nivolumab, pembrolizumab can be added to the subject's treatment regimen upon confirmation of progression and at the discretion of the Sponsor and investigator. Confirmatory scans may be performed no less than 4 weeks from the most recent radiographic assessment documenting disease progression.

Figure 6: Part C q3w Treatment Schema

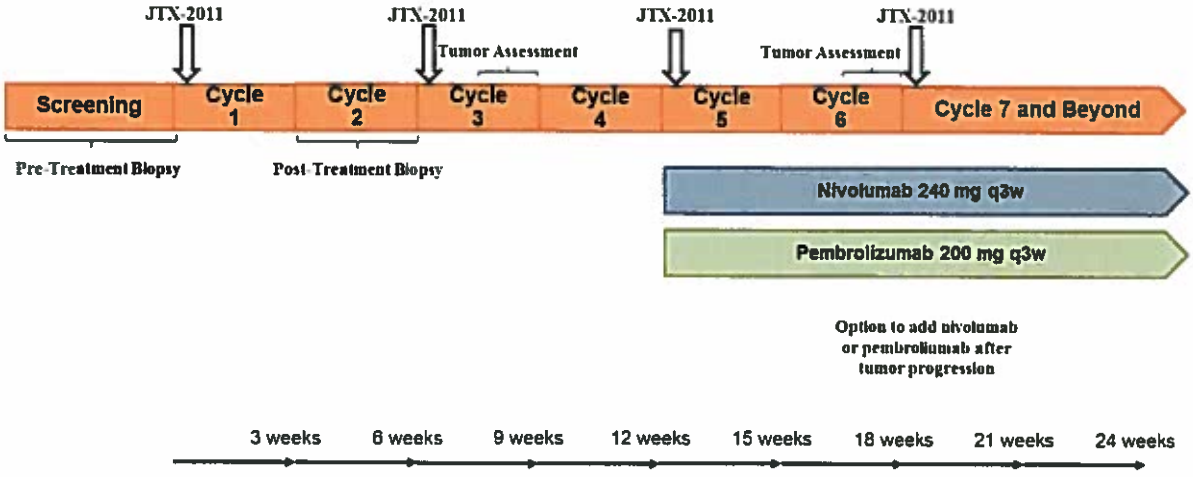
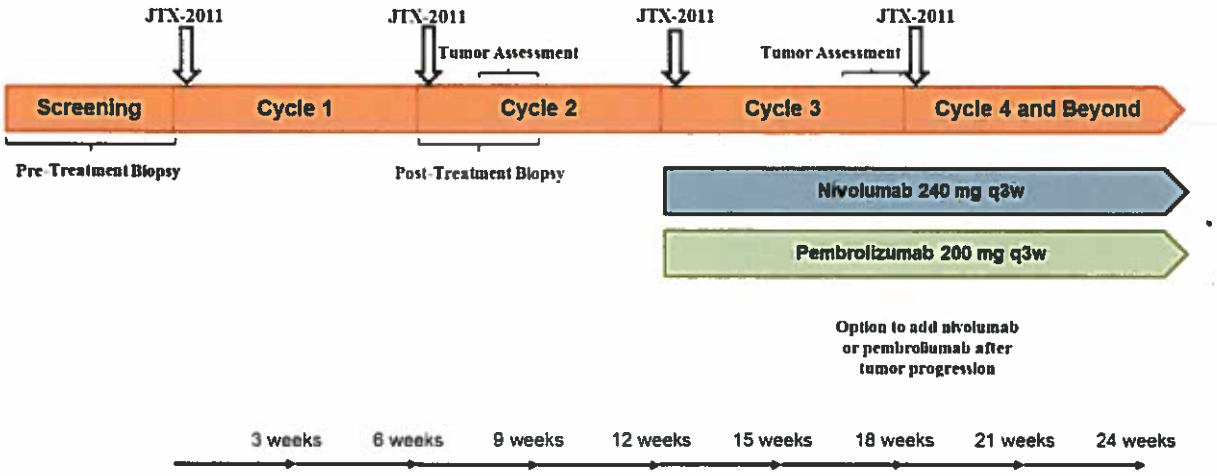


Figure 7: Part C q6w Treatment Schema



5.6. Part D (JTX-2011 in Combination with Nivolumab Combination Phase 2)

Part D will include approximately 15 subjects in each of 6 dose expansion cohorts (90 total subjects) in the indications listed below of JTX-2011 in combination with nivolumab at a JTX-2011 dose of 0.3 mg/kg:

<u>**q3w JTX-2011 + q3w nivolumab**</u>

- D01: HNSCC that has progressed on or after a prior PD-1 inhibitor
- D02: NSCLC that has progressed on or after a prior PD-1 inhibitor
- D03: TNBC
- D04: Melanoma that has progressed on or after a prior PD-1 inhibitor (*closed to enrollment*)
- D05: Gastric cancer or gastroesophageal junction adenocarcinoma
- D06: MSI-H or dMMR endometrial cancer (*closed to enrollment*)

The JTX-2011 dose in Part D is 0.3 mg/kg. Subjects in Part D expansion cohorts D01, D02, D03, D04, and D05 will be stratified based on ICOS expression by IHC in archival tumor, with ICOS levels confirmed on a fresh pre-treatment biopsy. At least 10 subjects with high (2+ to 3+) ICOS expression will be enrolled in each 15-subject cohort to explore potential correlation between pre-treatment ICOS expression and efficacy. More subjects may be enrolled to ensure a minimum 10 subjects with high ICOS expression. Additional potential predictive biomarkers will also be evaluated.

Fresh pre-treatment biopsies will be examined retrospectively to assess correlation of potential predictive biomarkers with efficacy.

5.7. Part F (JTX-2011 in Combination with Ipilimumab Phase 2)

Part F will include two (2) cohorts in the indications listed below (approximately 15 subjects each in cohorts F61-F62 (approximately 30 subjects), dosing JTX-2011 in combination with ipilimumab. The JTX-2011 dose level in Part F will be determined in Part E.

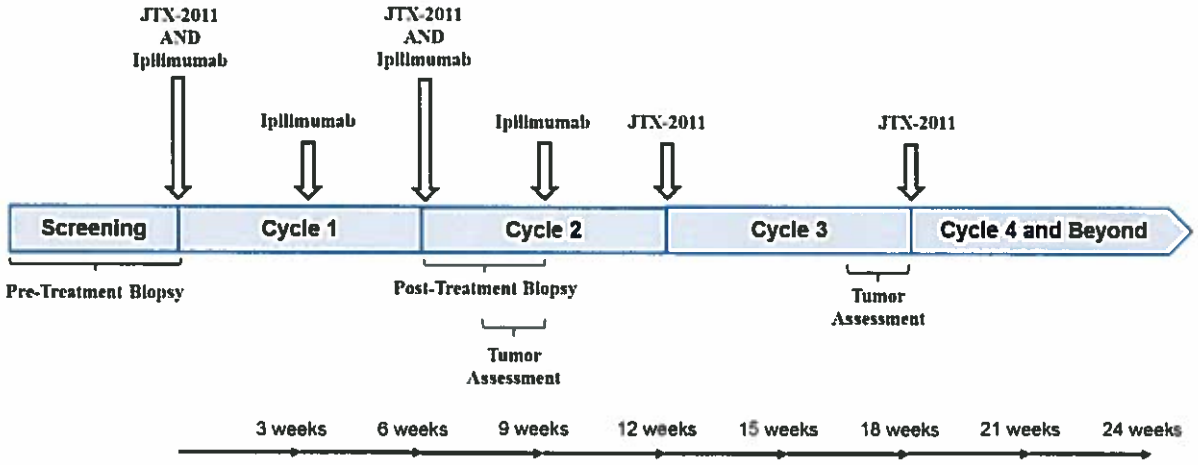
q6w JTX-2011 + up to 4 doses of Ipilimumab (q3w)

- F61: mCRPC that has progressed on or after treatment with at least one prior standard of care therapy;
- F62: Unresectable or metastatic melanoma with ≤ 2 prior lines of therapy in the unresectable or metastatic setting.

Pre-screening for ICOS will not be required. Subjects in Part F are required to have archival tumor and two fresh tumor biopsies (one during screening and one post-dose between C2D1 and C2D22). In situations where archival tissue is not available or biopsies are not feasible (e.g., would expose the subject to unreasonable health risks), one or more of these requirements may be waived after discussion with the Medical Monitor.

To complete enrollment in the Part F cohorts, at least 15 assessable pre-treatment fresh biopsies must have been obtained in each cohort.

Figure 8: Part F Treatment Schema



5.8. Part H (JTX-2011 in Combination with Pembrolizumab Combination Phase 2)

Part H will include six (6) cohorts in the indications listed below, dosing JTX-2011 at q3w in combination with pembrolizumab in Cohorts H31-H35 and q6w in combination with pembrolizumab in Cohort H64. Approximately 15 subjects will be enrolled in Cohorts H31-H33 and H35. Cohorts H34 and H64 are expansion cohorts and will each enroll approximately 49 subjects. All subjects must be immunotherapy naïve:

q3w JTX-2011 + q3w Pembrolizumab

- H31: recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy;
- H32: metastatic NSCLC that has high PD-L1 expression (TPS Score ≥ 50%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations;
- H33: metastatic or recurrent TNBC with ≤ 1 prior line of therapy in the metastatic or recurrent setting;

- H34: recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma, including adenocarcinoma of the lower esophagus with disease progression on or after 1 prior line of therapy, including HER2/neu-targeted therapy, if appropriate;
- H35: unresectable or metastatic MSI-H solid tumors that have progressed on prior FDA-approved treatment and who have no satisfactory alternative treatment options or MSI-H colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

q6w JTX-2011 + q3w Pembrolizumab

- H64: recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma, including adenocarcinoma of the lower esophagus with disease progression on or after 1 prior line of therapy, including HER2/neu-targeted therapy, if appropriate

Pre-screening for ICOS will not be required. Subjects in Part H are required to have archival tumor and a fresh tumor biopsy during screening. In situations where archival tissue is not available or biopsies are not feasible (e.g., would expose the subject to unreasonable health risks), one or more of these requirements may be waived after discussion with the Medical Monitor.

To complete enrollment in the HNSCC (H31), NSCLC (H32), TNBC (H33), and MSI-H solid tumor (H35) cohorts, at least 15 assessable fresh biopsies must have been obtained in each cohort, 10 of which must have an ICOS score ≥ 1. To complete enrollment in the gastric expansion cohorts (H34 and H64), approximately 49 assessable fresh biopsies must be obtained in each, 33 of which must have an ICOS score of ≥ 1.

Figure 9: Part H q3w Treatment Schema

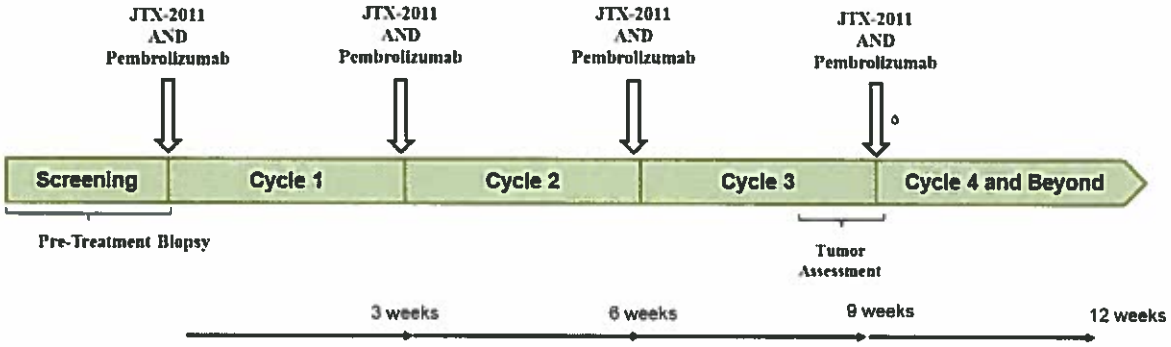
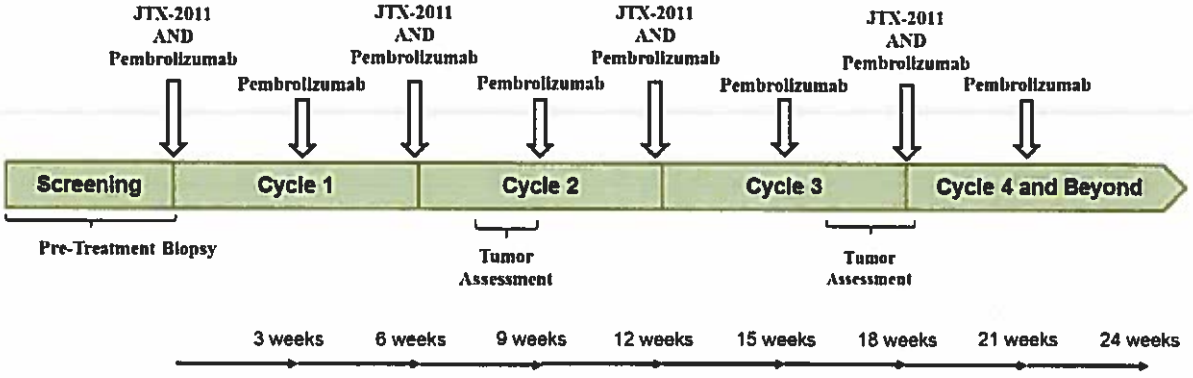


Figure 10: Part H q6w Treatment Schema



6. DOSE ESCALATION, MODIFICATION, AND PATIENT WITHDRAWAL

6.1. Safety Monitoring Committee

6.1.1. Dose Escalation

A Safety Monitoring Committee (SMC) composed of Investigators, study staff, Medical Monitor, and Sponsor representatives will review and approve all dose escalation decisions in Parts E and G. Dose escalation in Parts A and B have been completed with a recommended RP2D of 0.3 mg/kg q3w in both parts.

The SMC will review, at a minimum, the following safety data:

- Vital signs
- Clinical laboratory values
- Physical examination findings
- Adverse events/serious adverse events
- ECOG performance status

The SMC will hold a teleconference prior to dose escalations in Parts E and G. Based on the review of the data, the SMC will recommend that the study continue with escalation to the next dose, that an additional three subjects be enrolled at the current dose, or may alternatively recommend that the study be placed on hold, that the dose of study drug be de-escalated, or that the study be terminated. A recommendation of study hold, study drug dose de-escalation, or study termination would be made in the event of the discovery of an unexpected, serious, or unacceptable risk to the subjects in the study.

In addition, the SMC will review safety data for aggregate AEs for 9 weeks. Based on the review of the data, the SMC will recommend that the study continue as planned, or may alternatively recommend that the study be placed on hold, that the dose of study drug be de-escalated, or that the study be terminated. A recommendation of study hold, study drug dose de-escalation, or study termination would be made in the event of the discovery of an unexpected, serious, or unacceptable risk to the subjects in the study.

6.1.2. Ongoing Safety Review

Once dose escalation has been completed, the SMC will be convened approximately every 3 months to review accumulating safety data and subject disposition by cohort.

6.2. Dose Escalation Scheme

In Part A, six (6) dose escalation cohorts were explored, 0.003 mg/kg, 0.01 mg/kg, 0.03 mg/kg, 0.1 mg/kg, 0.3 mg/kg, and 1 mg/kg. In Part B, four (4) dose escalation cohorts were explored, 0.01 mg/kg, 0.03 mg/kg, 0.1 mg/kg, 0.3 mg/kg.

In Parts E and G, each dose escalation cohort will consist of a minimum of 3 subjects. The first subject in each dose cohort will receive JTX-2011 + ipilimumab or + pembrolizumab, respectively, on C1D1 (sentinel subject) and be monitored for at least 72 hours as an outpatient until acute and subacute safety is confirmed. If, after 72 hours, there are no safety concerns, the

next two subjects in the dose cohort will be allowed to enroll in parallel (if the Investigator and Sponsor agree, then no SMC review will be required). Note: hospitalization is not required).

If, after 72 hours, there are no safety concerns, the next two subjects in the dose cohort will be allowed to enroll in parallel (if the Investigator and Sponsor agree, then no SMC review will be required).

The first 3 or 6 subjects at each dose-level will be assigned according to the classical 3 + 3 design, as follows. If:

- 0 of 3 subjects in a cohort experiences a DLT, then the next higher dose-level cohort may be enrolled.
- 1 of 3 subjects in a cohort experiences a DLT, then enrollment into that cohort will be expanded to a total of 6 subjects.
- 1 of 6 subjects in an expanded cohort experiences a DLT, then the next higher dose-level cohort may be enrolled.
- >1 of 3-6 subjects in a cohort experience a DLT, then the MTD has been exceeded and further enrollment into that cohort will cease. Using the same criteria, additional cohorts may then be explored until the MTD has been determined, including intermediate doses.

Subjects in each cohort must complete the first cycle of each cohort through C2D1 assessments or have experienced a DLT to be considered evaluable; non-evaluable subjects will be replaced.

Once a RP2D is determined for a particular part of the trial, subjects at lower doses in that part who remain on study treatment and are tolerating it well may increase their dose to the RP2D. In addition, the SMC will be convened approximately every 3 months to review accumulating safety data and patient disposition by cohort through the duration of the study.

6.2.1. Initiation of Parts C, D, F, and H

Part C

Assuming that there are no safety concerns in Part A, enrollment in Part C will begin once a dose is identified from Part A that results in approximately 70% sustained ICOS TE through day 21 and PK that support dosing q3w or q6w or the MTD is identified. This is anticipated to be one dose level above the dose level selected for Safety/PK/PD Expansion cohort AP1.

Part D

Assuming that there are no safety concerns in Part B, enrollment in Part D will begin once a dose is identified from Part B that results in approximately 70% sustained ICOS TE and PK that support dosing q3w or the MTD is identified. This is anticipated to be one dose level above the dose level selected for Safety/PK/PD Expansion cohort BP1.

Part F

Enrollment in Part F will begin assuming that there are no safety concerns and the RP2D has been determined from Part E.

Part H

Enrollment in Part H will begin assuming that there are no safety concerns and the RP2D has been confirmed from Part G.

6.2.2. Criteria for Proceeding to the Next Dose Level

Depending upon the dosing schedule being tested in dose escalation, the Safety Monitoring Committee (SMC) will review all safety data available through at least 2 weeks (in q3w dosing) or 5 weeks (q6w dosing) and make an initial dose escalation recommendation. Enrollment in the next dose escalation cohort may occur after:

- SMC determines that that there are no safety concerns with review of ≥ 14 days data for all evaluable subjects within a cohort;
- All subjects within a dose cohort complete ≥ 1 cycle;
- DLT observed in < 1 out of 3 evaluable subjects (or < 2 out of 6 evaluable subjects) during Cycle 1;
- SMC agrees that no additional subjects are required in the current cohort to further define safety.

Following the review of safety data obtained at a given dose level, the SMC will convene via telephone conferences and decide the dose level for the next cohort. If potential safety signals are identified, the administration of interim dose levels (e.g., increment of < 25% of current dose level instead of 25-50%) may be recommended. In addition, to enable accurate and appropriate clinical and scientific interpretation of the data, a dose level may be repeated as requested by the SMC. Dose escalation will be recommended only if a consensus to escalate is reached by the SMC after review and discussion of the current dose level's safety data.

6.3. Definition of Dose Limiting Toxicity (DLT)

A DLT is defined as any of the following study drug-related toxicities (defined as at least possibly related to study drug) **occurring in the first cycle** of study treatment:

Hematological:

- ≥ Grade 4 neutropenia lasting > 7 days;
- Febrile neutropenia;
- Any Grade 3 thrombocytopenia with bleeding or a requirement for platelet transfusions;
- ≥ Grade 4 thrombocytopenia (platelets < 25,000/μL).

Non-hematological:

- AST or ALT > 3 x ULN and concurrent total bilirubin > 2 x ULN without initial findings of cholestasis (e.g. findings consistent with Hy's law or FDA definition of potential drug-induced liver injury [pDILI]);
- ≥ Grade 4 AST or ALT of any duration;
- Any ≥Grade 3 non-hematologic toxicity with the following exceptions:
    - Grade 3 immune-related AE (irAE) that resolves to ≤ Grade 1 or to baseline with immunosuppressive therapy within 3 weeks;
    - Grade 3 fatigue that persists < 7 days;
    - Grade 3 rash that resolves to ≤ Grade 1 within 3 weeks;
    - Grade 3 or 4 elevation in serum amylase and/or lipase that are not associated with clinical or radiographic evidence of pancreatitis;

- ≥ Grade 3 electrolyte abnormality that lasts < 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical intervention;
- Grade 3 nausea or vomiting that lasts < 48 hours, and resolves to ≤ Grade 1 either spontaneously or with conventional medical intervention;
- Grade 3 infusion reaction that resolves within 6 hours to ≤ Grade 1;
- Alopecia;
- Grade 3 endocrinopathy that is adequately controlled by hormone replacement;
- Grade 3 tumor flare.

- Any Grade 4 or 5 Adverse Event (AE);
- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks OR requires systemic treatment;
- Any treatment-related Grade 2 or greater toxicity that persists and results in an inability to administer C2D1.

For events that are not included in the above definitions, the SMC may declare any additional specific toxicity to be a DLT.

If a subject experiences a DLT which subsequently resolves to baseline and does not automatically meet the criteria for study discontinuation (e.g., Grade 4 AST or ALT), the Sponsor in conjunction with the Investigator and/or SMC, may decide if the subject is allowed to stay on study treatment and resume treatment at a lower dose.

6.4. Rules for Suspension of Dose Escalation

The SMC will recommend termination of dose escalation if any of the DLT conditions (see Section 6.2.2) are met in ≥ 2 of up to 6 subjects in a cohort. The SMC may also recommend suspension of JTX-2011 dose escalation based upon other conditions as deemed medically appropriate.

6.5. Safety/PK/PD Expansion Cohorts (AP1, AP2, BP1, BP2)

At each of two or more dose levels, approximately eight additional subjects will be enrolled for additional safety and PK/PD data. These subjects will be required to have biopsies of their tumors at baseline and after completion of 2 cycles of JTX-2011 for pharmacodynamics assessments. These subjects may be enrolled before, during, and after enrollment has commenced in Part C or D.

First Safety/PK/PD Expansion Cohort: If safety data are acceptable, Part A Safety/PK/PD Expansion Cohort 1 (AP1) and Part B Safety/PK/PD Expansion Cohort 1 (BP1) will be initiated at the first dose level of that Part at which there is approximately 70% Target Engagement (TE) in 2/3 subjects on Day 8.

Second Safety/PK/PD Expansion Cohort: If safety data are acceptable, Part A Safety/PK/PD Expansion Cohort 2 (AP2) and Part B Safety/PK/PD Expansion Cohort 2 (BP2) will be initiated at the lowest dose level at which there is approximately 70% TE in 2/3 subjects on Day 21, the MTD, or the highest dose studied.

The SMC will review safety data as outlined in the dose escalation phase for aggregate AEs for 9 weeks (e.g. through Cycle 3). Once a RP2D is determined, subjects at lower doses who remain on study treatment and are tolerating it well may increase their dose to the RP2D. In addition, the SMC will be convened approximately every 3 months to review accumulating safety data and patient disposition by cohort through the duration of the study.

6.6. Definition of Maximum Tolerated Dose and Recommended Phase 2 Dose

The MTD is defined as the JTX-2011 dose level that yields the largest estimated toxicity rate below 33%.

The RP2D, as well as administration time (currently a one-hour IV infusion each for JTX-2011 and nivolumab, 1.5-hour infusion for ipilimumab, and 30-minute infusion for pembrolizumab) and schedule will be determined in discussion among the Sponsor and Investigators. Observations related to safety, PK, pharmacodynamics, and IV infusion tolerability will be included in the rationale supporting the RP2D and schedule.

Observations related to safety, PK, pharmacodynamics, and IV infusion tolerability will be included in the rationale supporting the RP2D and schedule.

6.7. Criteria for Dose Modifications

6.7.1. Delayed Cycles

A change in the start of a cycle of +3 days for social reasons (e.g., holidays) is permitted if unavoidable. Subjects who require frequent treatment delays should be discussed with the Medical Monitor.

Subjects requiring a delay of a scheduled cycle starting on or after Cycle 3 due to treatment-related toxicities that have not resolved are to be managed as follows:

- If the delay is ≤ 7 days, treatment should resume at the assigned dose level.
- If the delay is > 7 days but ≤14 days, treatment should resume at the next lower dose level.
- If the delay is more than 14 days, further course of treatment should be discussed with the Medical Monitor.

If a cycle delay of >14 days not due to treatment-related toxicity occurs, the circumstances surrounding the delay will be discussed with the Medical Monitor prior to dosing the patient for the next cycle.

6.7.2. Dose Interruptions

For study drug interruptions that occur for non-drug-related complications, the subject will remain on study as long as the study drug is infused within 6-hours of the interruption. If the interruption is due to toxicity, please refer to Section 6.7.3for dose modifications.

6.7.3. Dose Modifications

6.7.3.1. Dose Modifications for JTX-2011

During dose-escalation, dose modifications are not allowed during Cycle 1, unless the subject experiences an infusion related reaction during the first administration of JTX-2011 which prevents the patient from receiving the first dose in its entirety. If, during the first dose, a subject experiences an infusion reaction where the Investigator determines the infusion should be terminated prematurely as a safety precaution, the event should be treated as a DLT according to Protocol Section 6.3.

The Investigator should then consult the Jounce Medical Monitor to determine if the patient should be either discontinued from the study, or proceed with future modified infusions (e.g., slower rate, lower dose group). Any AE that is severe enough (at the discretion of the Investigator and with permission of the Sponsor/CRO Medical Monitor) to warrant a dose reduction during Cycle 1 will be considered a DLT.

Dose Modifications and Management of Toxicity for JTX-2011 is provided in Table 5.

Table 5: Dose Modifications and Toxicity Management for JTX-2011, Nivolumab, Ipilimumab and Pembrolizumab

Adverse Event	Severity	Dose Modification	Recommended Management[a]
Diarrhea or Colitis	Grade 2	Withhold study drug(s) until symptoms resolved to Grade 0-1. If occurring in combination with nivolumab, ipilimumab or pembrolizumab, when symptoms resolved to Grade 0-1, resume JTX-2011. If symptoms do not recur after 1 cycle of JTX-2011, resume combination.[c] Permanently discontinue ipilimumab if symptoms last 6 weeks or longer or inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day	If symptoms persist > 5 days or recur: 0.5 to 1 mg/kg/day prednisone equivalents followed by steroid taper[a]
	Grade 3	Withhold study drug(s) until symptoms resolved to Grade 0-1. If occurring in combination with nivolumab or pembrolizumab, when symptoms resolved to Grade 0-1, resume JTX-2011. If symptoms do not recur after 1 cycle of JTX-2011, resume combination. Permanently discontinue if in combination with ipilimumab	1-2 mg/kg/day prednisone equivalents followed by steroid taper[a]
	Grade 4	Permanently discontinue	1-2 mg/kg/day prednisone equivalents followed by steroid taper[a]
Pneumonitis	Grade 2	Withhold study drug(s) until resolved to Grade 0-1 If occurring in combination with nivolumab, ipilimumab or pembrolizumab, when symptoms resolved to Grade 0-1, resume JTX-2011. If symptoms do not recur after 1 cycle of JTX-2011, resume combination.[c] Permanently discontinue study drugs if recurrent grade 2 pneumonitis in combination with pembrolizumab Permanently discontinue ipilimumab if symptoms last 6 weeks or longer	1-2 mg/kg/day prednisone equivalents followed by steroid taper[a]

	Grade 3 or 4	Permanently discontinue	1-2 mg/kg/day prednisone equivalents followed by steroid taper[a]
Hepatitis	Grade 2 AST/ALT (>3 to 5 × ULN) or bilirubin (1.5 to 3 × ULN)[b]	Withhold study drug(s) until resolved to Grade 0-1. If occurring in combination with nivolumab, ipilimumab or pembrolizumab, when symptoms resolved to Grade 0-1, resume JTX-2011. If symptoms do not recur after 1 cycle of JTX-2011, resume combination.[c] Permanently discontinue ipilimumab if symptoms last 6 weeks or longer	0.5 to 1 mg/kg/day prednisone equivalents or investigator discretion[a]
	Grade 3 or 4 AST/ALT (>5 × ULN) or bilirubin (>3 x ULN)[b]	Permanently discontinue	1-2 mg/kg/day prednisone equivalents or investigator discretion[a]
Hypophysitis	Grade 2 or 3	Withhold study drug(s) until resolved to Grade 0-1 If occurring in combination with nivolumab, ipilimumab or pembrolizumab, when symptoms resolved to Grade 0-1, resume JTX-2011. If symptoms do not recur after 1 cycle of JTX-2011, resume combination.[c] If occurring in combination with ipilimumab, permanently discontinue study drugs if symptomatic endocrinopathy lasts 6 weeks or longer or if there's inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day	1 mg/kg/day prednisone equivalents[a]
	Grade 4	Permanently discontinue if not manageable with medical treatment	1 mg/kg/day prednisone equivalents[a]
Adrenal insufficiency	Grade 2	Withhold study drug(s) until resolved to Grade 0-1 If occurring in combination with nivolumab, ipilimumab or pembrolizumab, when symptoms resolved to Grade 0-1, resume JTX-2011. If symptoms do not recur after 1 cycle of JTX-2011, resume combination.[c]	Observation

		If occurring in combination with ipilimumab, permanently discontinue study drugs if symptomatic endocrinopathy lasts 6 weeks or longer or if there's inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day	
	Grade 3 or 4	Permanently discontinue if not manageable with medical treatment[b].	1-2 mg/kg/day prednisone equivalents. Stress dose of IV steroid with mineralocorticoid activity if adrenal crisis suspected[a]
Thyroid disorders	Hypothyroidism	No study drug(s) adjustment If Grade 3 or 4 hypothyroidism occurs in combination with pembrolizumab or if symptomatic hypothyroidism occurs in combination with ipilimumab, withhold study drugs. Resume JTX-2011 upon resolution of hypothyroidism to Grade 0-1. If symptoms do not recur after 1 cycle of JTX-2011, resume combination. Permanently discontinue study drugs if symptomatic endocrinopathy in combination with ipilimumab lasts 6 weeks or longer or if there's inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day	Hormone replacement therapy
	Hyperthyroidism	No study drug(s) adjustment If Grade 3 or 4 hyperthyroidism occurs in combination with pembrolizumab or if symptomatic hypothyroidism occurs in combination with ipilimumab, withhold study drugs. Resume JTX-2011 upon resolution of hyperthyroidism to Grade 0-1. If symptoms do not recur after 1 cycle of JTX-2011, resume combination. Permanently discontinue study drugs if symptomatic endocrinopathy in combination with ipilimumab lasts 6 weeks or longer or if there's inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day	Medical management.
Type 1 Diabetes Mellitus	Grade 3 hyperglycemia	Withhold study drug(s) until metabolic control is achieved with insulin. Resume JTX-2011 upon resolution of hyperglycemia to Grade 0-1. If symptoms do not recur after 1 cycle of JTX-2011, resume combination.	Administer insulin until metabolic control is achieved.

		Permanently discontinue study drugs if symptomatic endocrinopathy in combination with ipilimumab lasts 6 weeks or longer or if there's inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day	
	Grade 4 hyperglycemia	Permanently discontinue if not manageable with medical treatment. Permanently discontinue study drugs if symptomatic endocrinopathy in combination with ipilimumab lasts 6 weeks or longer or if there's inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day	Administer insulin
Nephritis and Renal Dysfunction	Grade 2: serum creatinine (>1.5 to 3 × ULN)	Withhold study drug(s) until resolution to Grade 0-1 If occurring in combination with nivolumab, ipilimumab or pembrolizumab, when resolved to Grade 0-1, resume JTX-2011. If increase in serum creatinine does not recur after 1 cycle of JTX-2011, resume combination.[c]	0.5 to 1 mg/kg/day prednisone equivalents followed by steroid taper. If worsening or no improvement occurs, increase dose of corticosteroids to 1-2 mg/kg/day prednisone equivalents and permanently discontinue.[a]
	Grade 3: serum creatinine (>3 to 6 x ULN)	If occurring with monotherapy or in combination with nivolumab, withhold study drug(s). When resolved to Grade 0-1, resume JTX-2011. If increase in serum creatinine does not recur after 1 cycle of JTX-2011, resume combination, if applicable. Permanently discontinue study drugs if occurring in combination with pembrolizumab or ipilimumab	1-2 mg/kg/day prednisone equivalents[a]
	Grade 4: serum creatinine (>6 x ULN)	Permanently discontinue	1-2 mg/kg/day prednisone equivalents[a]
Rash	Grade 2	Only if occurring in combination with ipilimumab, withhold study drugs. When symptoms resolve to Grade 0-1, resume JTX-2011. If symptoms do not recur after 1 cycle of JTX-2011, resume combination.[c]	0.5 to 1 mg/kg/day prednisone equivalents[a]

	Grade 3	Withhold study drug(s) until resolution to Grade 0-1. If occurring in combination with nivolumab or pembrolizumab, when symptoms resolved to Grade 0-1, resume JTX-2011. If symptoms do not recur after 1 cycle of JTX-2011, resume combination. Permanently discontinue if in combination with ipilimumab	1-2 mg/kg/day prednisone equivalents[a]
	Grade 4	Permanently discontinue	1-2 mg/kg/day prednisone equivalents[a]
Neuropathy	Grade 2	Withhold study drug(s) until resolved to Grade 0-1; if symptoms persist ≥ 6 weeks, subject continuation discussed between PI and Medical Monitor If occurring in combination with nivolumab, ipilimumab or pembrolizumab, when symptoms resolved to Grade 0-1, resume JTX-2011. If symptoms do not recur after 1 cycle of JTX-2011, resume combination.[c] If occurring in combination with ipilimumab, permanently discontinue study drugs for related reactions lasting 6 weeks or longer or inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day	None
	Grade 3	Withhold study drug(s) until resolved to Grade 0-1; if symptoms persist ≥ 6 weeks subject continuation discussed between PI and Medical Monitor If occurring in combination with nivolumab or pembrolizumab, when symptoms resolved to Grade 0-1, resume JTX-2011. If symptoms do not recur after 1 cycle of JTX-2011, resume combination. Permanently discontinue study drugs if occurred in combination with ipilimumab	1-2 mg/kg/day prednisone equivalents[a]
	Grade 4	Permanently discontinue	1-2 mg/kg/day prednisone equivalents[a]

Encephalitis	New-onset moderate or severe neurologic signs or symptoms	Permanently discontinue	If etiologies other than immune-mediated adverse event are ruled out, permanently discontinue JTX-2011 and administer 1-2 mg/kg/day prednisone equivalents[a]
	Immune-mediated encephalitis	Permanently discontinue	1-2 mg/kg/day prednisone equivalents[a]
Ophthalmologic	Uveitis, iritis, or episcleritis	Permanently discontinue if not resolved to Grade 0-1 with local immunosuppressive therapy	Corticosteroid eye drops
Other	Other Grade 3 adverse reaction	Withhold study drug(s) until resolution to Grade 0-1. If occurring in combination with nivolumab or pembrolizumab, when symptoms resolved to Grade 0-1, resume JTX-2011. If symptoms do not recur after 1 cycle of JTX-2011, resume combination. Permanently discontinue study drugs if occurring in combination with ipilimumab	Consider 1-2 mg/kg/day prednisone equivalents[a]
	Recurrence of same Grade 3 adverse reaction	Subject continuation discussed between PI and Medical Monitor	1-2 mg/kg/day prednisone equivalents[a]
	Life threatening or Grade 4 adverse reaction	Permanently discontinue	1-2 mg/kg/day prednisone equivalents[a]
	Requirement for 10 mg prednisone per day or greater prednisone or equivalent for > 12 weeks	Permanently discontinue	
	Persistent Grade 2 or 3 adverse reaction lasting ≥ 12 weeks	Subject continuation discussed between PI and Medical Monitor	

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal.
Toxicity graded per National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 (NCI CTCAE v4.03)
[a]If steroids have been administered, taper steroids per institution guidelines
[b] Subjects with liver metastasis who begin combination therapy with pembrolizumab with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week, discontinue study drugs
[c] Patients must have partial resolution of symptoms (Grade 0-1) and must be receiving less than 7.5mg of prednisone or equivalent per day in order to resume treatment with ipilimumab

6.7.3.2. Dose Modifications and Toxicity Management for JTX-2011 in Combination with Nivolumab

For dose modifications for nivolumab please follow the prescribing information (Opdivo® Full Prescribing Information{Bristol-Myers Squibb Company 2017a}). In the event of a toxicity that requires that study treatment be withheld until resolution to Grade 0 or 1, the first administration of study drug after resolution of toxicity should be JTX-2011 alone. Nivolumab may be added at the next dose, at the discretion of the investigator and the medical monitor, if the toxicity does not recur with JTX-2011 monotherapy.

6.7.3.3. Dose Modifications and Toxicity Management for JTX-2011 in Combination with Ipilimumab

For dose modifications for ipilimumab please follow the prescribing information (Yervoy® Full Prescribing Information{Bristol-Myers Squibb Company 2017b}). In the event of a toxicity that requires that study treatment be withheld until resolution to Grade 0 or 1, the first administration of study drug after resolution of toxicity should be JTX-2011 alone. Ipilimumab may be added at the next dose, at the investigator's discretion, if the toxicity does not recur with JTX-2011 monotherapy.

6.7.3.4. Dose Modifications and Toxicity Management for JTX-2011 in Combination with Pembrolizumab

For dose modifications for pembrolizumab please follow the prescribing information (Keytruda® Full Prescribing Information {Merck & Co Inc 2017}). In the event of a toxicity that requires that study treatment be withheld until resolution to Grade 0 or 1, the first administration of study drug after resolution of toxicity should be JTX-2011 alone. Pembrolizumab may be added at the next dose, at the investigator's discretion, if the toxicity does not recur with JTX-2011 monotherapy.

6.7.4. Infusion-Related Reactions

Subjects must be observed for at least 1 hour after completion of infusion of JTX-2011, nivolumab, ipilimumab, and pembrolizumab. In the event of acute hypersensitivity or other infusion reaction, institutional protocol should be initiated and a blood sample drawn for cytokines (NOTE: To be collected at the site and sent out to a Central Laboratory for analysis. Please reference Lab Manual for more details). Signs and symptoms of an infusion reaction may include the following: headache, fever, facial flushing, pruritus, myalgia, nausea, chest tightness, dyspnea, vomiting, erythema, abdominal discomfort, diaphoresis, shivers, hypertension, hypotension, lightheadedness, palpitations, urticaria and somnolence. Although unlikely, serious allergic reactions (e.g., anaphylaxis) may occur at any time during the infusion.

6.7.4.1. Grade 2 Infusion-Related Reactions

In the case of Grade 2 occurrence of signs and symptoms consistent with infusion related reaction, follow institutional protocol and reduce the rate of infusion of JTX-2011 to half the initial rate; consider interrupting infusion of JTX-2011 if symptoms do not respond to medical intervention. If signs and symptoms resolve with intervention including interruption of JTX-2011, JTX-2011 infusion may be restarted at half the initial rate.

6.7.4.2. Grade 3 Infusion-Related Reactions

In the case of Grade 3 or greater occurrence of signs and symptoms consistent with infusion related reaction, discontinue infusion of JTX-2011.

6.7.4.3. Infusion- Related Reaction Prophylaxis

No prophylaxis for infusion related reactions should be administered prior to the Cycle 1 Day 1 dose of study drug. For subjects that experience a Grade 2 or 3 infusion-related reaction and remain on treatment, institutional practice for prevention of infusion reactions should be followed for all subsequent cycles.

Once the Phase 2 cohorts for any part of the trial have been initiated, the Sponsor may administratively allow for infusion reaction prophylaxis (as per institutional guidelines) beginning prior to study drug dosing on C1D1.

6.8. Withdrawal of Subjects

A subject is free to withdraw from treatment or from follow-up at any time for any reason without prejudice to their future medical care by the physician or at the institution. However, subjects who withdraw from treatment should be encouraged to return for the end-of-treatment visit, complete all safety assessments, and enter long-term follow-up. If a subject refuses to undergo the end-of-treatment procedures, the reason for refusal should be fully documented in the patient's electronic Case Report Form (eCRF). Subjects who withdraw from follow-up should not be followed for any of the visits and assessments described above.

The Investigator or Jounce may also withdraw the subject from treatment at any time in the interest of his or her safety. The primary reason for withdrawal must be recorded in the subject's medical record and on the withdrawal form in the eCRF. If a subject is withdrawn for more than one reason, each reason should be documented in the source document and the most medically significant reason should be entered on the eCRF.

The withdrawal of a subject from treatment should be discussed where possible with the Medical Monitor before the subject stops taking study drug. If study treatment is discontinued, the final evaluations will be performed as completely as possible.

The reason for termination, date of stopping study treatment and the total treatment period must be recorded in the eCRF and source documents.

6.8.1. Criteria for Withdrawal

The Medical Monitor may be contacted on a case-by-case basis if clarification is required. Reasons for withdrawal include:

- Withdrawal of consent by the subject or refusal by the subject to continue treatment and/or procedures/observations;
- Radiographic or clinical disease progression with or without a requirement for alternative treatment for the condition under study;
- Occurrence of unmanageable adverse events in the judgment of the Investigator or subject, justifies withdrawal due to its severity, nature, or requirement for treatment, regardless of the causal relationship to study drug;

- Pregnancy;
- If the Investigator feels it is in the subject's best interest to withdraw;
- Other reasons (e.g., significant protocol violation, non-compliance, lost to follow-up);
- Termination of the study by Sponsor.

6.8.2. Subject Replacement

Subjects enrolled in Parts A, B, E or G dose escalation cohorts who withdraw from treatment or are lost-to-follow-up prior to completion of Cycle 2 Day 1 assessments will need to be replaced, unless the subject has experienced a DLT.

6.9. Pre-Screening for ICOS Expression

Subjects who have archival biopsy samples available for submission to the central lab for measurement of ICOS expression may provide informed consent for submission of archival samples for evaluation prior to undergoing the informed consent process and screening for full study participation. A separate abbreviated Informed Consent Form will be provided to sites to utilize for this purpose upon approval by their governing IRB. In situations where a subject's archival samples are completely exhausted, subjects may elect to have a biopsy performed per institutional guidelines to serve as an archival sample. Results from ICOS testing of archival tissue performed prior to the 28-day screening window will not need to be repeated.

7. OVERALL STUDY ASSESSMENTS AND FOLLOW-UP

The total study duration is anticipated to be 24-30 months. Each subject's participation on treatment will last a minimum of approximately 3-4 months, including:

- Up to a 28-day screening period;
- 1 cycle (3 or 6 weeks) of study treatment. However, subjects may continue to receive additional cycles of study treatment as long as, in the judgement of the Investigator, the subject may be deriving clinical benefit;
- End of Treatment visit performed 28 days (± 7 days) after the last dose of study treatment;

7.1. Screening (All Parts)

Subject eligibility for the study will be determined ≤ 28 days prior to initiating study treatment.

The following clinical assessments will be performed during screening:

- Signing of informed consent form.
- Review of eligibility criteria. Eligibility should be confirmed prior to the first dose of study drug(s).
- Subject medical history, disease history, demographics, physical examination including vital signs, height, and weight.
- ECOG performance status assessment.
- Laboratory Assessments: Chemistry, hematology, coagulation, thyroid function and urinalysis.
- Blood samples for Immunophenotyping and Target Engagement.
- 12-lead ECG.
- Ensure archival tumor tissue is available if not already required for pre-screening.
- Radiologic assessment (within 28 days prior to C1D1). CT scan is preferred; however, whichever modality is used at screening should be repeated throughout the trial.
- Optional Brain MRI to confirm stable brain metastasis.
- Record concomitant medications.
- Serum or urine pregnancy test for women of child-bearing potential (WOCBP). The pregnancy test will not be required for women who are surgically sterile or who are greater than 1 year post-menopausal.
- AP1, AP2, BP1, BP2, Parts C, D, F, G, and H only:
  - Fresh tumor tissue biopsy prior to dosing on C1D1.
- Prostate cancer subjects in Parts E and F only:
  - Bone Scan.

7.2. Treatment Period

7.2.1. Cycle 1 Day 1 (All Parts)

The following evaluations and procedures will be performed during this visit:

Any assessments or labs that were performed or obtained within 72 hours of Cycle 1 Day 1 do not need to be repeated.

- Physical examination;
- Vital signs pre-and post-infusion;
- Weight;
- ECOG performance status;
- Pregnancy test for WOCBP;
- 12-lead ECG;
- Laboratory assessments including chemistry, hematology, coagulation, thyroid function, and urinalysis;
- Blood samples for PK/ADA/NAb, Cytokines, Immunophenotyping, Target Engagement, RNA and DNA;
- Record concomitant medications;
- Adverse events assessment;
- JTX-2011 administration followed by observation for at least 1 hour;
- Parts B and D only:
  - Nivolumab administration followed by observation for at least 1 hour;
- Parts E and F only:
  - Ipilimumab administration followed by observation for at least 1 hour;
  - PSA
- Parts G and H only:
  - Pembrolizumab administration followed by observation for at least 1 hour.

7.2.2. Cycle 1 Day 2 (All Parts)

The following evaluations and procedures will be performed during this visit:

- Vital signs;
- Blood sample for PK, Cytokines, Immunophenotyping, Target Engagement;
- Record concomitant medications;
- Adverse events assessment.

7.2.3. Cycle 1 Day 4 (Part A, B, E, and G Sentinel Subjects Only)

- Targeted Physical Exam (as per institutional guidelines);
- Vital signs;
- Record concomitant medications;
- Adverse events assessment.

7.2.4. Cycle 1 Day 8 (Parts A, B, E, and G only, including AP1, AP2, BP1, BP2)

The following evaluations and procedures will be performed during this visit:

- Vital signs;
- Targeted Physical Exam (as per institutional guidelines)

- Laboratory Assessments: Chemistry, Hematology, Coagulation;
- Blood samples for PK, Immunophenotyping, and Target Engagement;
- Record concomitant medications;
- Adverse events assessment.

7.2.5. Cycle 1 Day 15 (Parts A and B [inc. AP1, AP2, BP1, BP2], E, and G only)

The following evaluations and procedures will be performed during this visit:

- Vital signs;
- Laboratory Assessments: Chemistry, Hematology, Coagulation;
- Blood samples for PK and Target Engagement;
- Record concomitant medications;
- Adverse events assessment.

7.2.6. Cycle 1 Day 22 (All cohorts in Parts E and F, q6w cohorts only in Parts C and H)

The following evaluations and procedures will be performed during this visit:

- Targeted Physical Exam.
- Laboratory Assessments: Chemistry, Hematology, Coagulation.
- Blood samples for PK/ADA/NAb, Cytokines, Immunophenotyping, Target Engagement.
- Record concomitant medications.
- Adverse events assessment.
- Part C (q6w) only:
  - Vital signs.
- Parts E and F only:
  - Weight.
  - Vital signs pre-and post-infusion.
  - Ipilimumab administration followed by observation for at least 1 hour.
- Part H only:
  - Weight.
  - Vital signs pre-and post-infusion.
  - Pembrolizumab administration followed by observation for at least 1 hour.

7.2.7. Cycle 2 Day 1 (All Parts)

The following evaluations and procedures will be performed during this visit (± 3 days):

- Targeted physical examination.
- Vital signs pre-and post-infusion.
- Weight.
- ECOG performance status.
- Pregnancy test for WOCBP.
- 12-lead ECG.

- Laboratory assessments: Chemistry, hematology, coagulation, thyroid function, and urinalysis. Laboratory assessments need not be repeated if they were performed within 72 hours of Cycle 2 Day 1.
- Blood samples for PK/ADA/NAb, Cytokines, Immunophenotyping, Target Engagement, and RNA.
- Record concomitant medications.
- Adverse events assessment.
- JTX-2011 Administration followed by observation for at least 1 hour.
- AP1, AP2, BP1, BP2, Parts C and F only:
  - Post-treatment fresh tumor biopsy
    - For q3w subjects: (Any timepoint after the C2D1 JTX-2011 dose and prior to the C3D1 JTX-2011 dose.
    - For q6w subjects: Any timepoint after the C2D1 JTX-2011 dose and prior to C2D22
- Parts B and D only:
  - Nivolumab administration followed by observation for at least 1 hour.
- Parts E and F only:
  - Ipilimumab administration followed by observation for at least 1 hour.
- Prostate cancer subjects in Parts E and F only:
  - Bone Scan.
- Parts G and H only:
  - Pembrolizumab administration followed by observation for at least 1 hour.

7.2.8. Cycle 2 Day 22 (All cohorts in Parts E and F, q6w cohorts only in Parts C and H)

The following evaluations and procedures will be performed during this visit (± 3 day):

- Physical examination;
- Laboratory Assessments: Chemistry, Hematology, Coagulation;
- Blood samples for PK/ADA/NAb, Target Engagement, and Immunophenotyping;
- Record concomitant medications.
- Adverse events assessment.
- Part C only:
  - Vital signs.
- Parts E and F only:
  - Weight.
  - Vital signs pre-and post-infusion.
  - Ipilimumab administration followed by observation for at least 1 hour.
- Part H only:
  - Weight.
  - Vital signs pre-and post-infusion.
  - Pembrolizumab administration followed by observation for at least 1 hour.

7.2.9. Cycle 3 Day 1 and Day 1 of Subsequent Cycles (All Parts)

The following evaluations and procedures will be performed during this visit (± 3 days):

- Physical examination.
- Vital signs pre-and post-infusion.
- Weight.
- ECOG performance status.
- Pregnancy test for WOCBP.
- 12-lead ECG.
- Laboratory assessments: Chemistry, hematology, coagulation, thyroid function, and urinalysis. Laboratory assessments need not be repeated if they were performed within 72 hours of Cycle 3 Day 1 or subsequent Day 1s.
- Blood samples for PK/ADA/NAb, Cytokines, Target Engagement, and Immunophenotyping.
- Blood sample for RNA (at Cycle 4 for q6w cohorts or Cycle 7 for q3w cohorts).
- Record concomitant medications.
- Adverse events assessment.
- JTX-2011 administration followed by observation for at least 1 hour.
- Parts B and D only:
  - Nivolumab Administration followed by observation for at least 1 hour.
- Parts E and F only:
  - Ipilimumab Administration followed by observation for at least 1 hour.
- Prostate cancer subjects in Parts E and F only:
  - PSA.
- Parts G and H only:
  - Pembrolizumab administration followed by observation for at least 1 hour.

7.2.10. Cycle 3 Day 22 and Day 22 of Subsequent Cycles (All cohorts in Parts E and F, q6w cohorts only in Parts C and H)

The following evaluations and procedures will be performed during this visit (± 3 day):

- ECOG performance status.
- 12-lead ECG.
- Laboratory Assessments: Chemistry, Hematology, Coagulation.
- Blood samples for PK/ADA/NAb, Target Engagement, and Immunophenotyping.
- Record concomitant medications.
- Adverse events assessment.
- Parts C, E, and F only:
  - Vital signs
- Part H only:
  - Weight.
  - Vital signs pre-and post-infusion.

- Pembrolizumab administration followed by observation for at least 1 hour.

7.2.11. Response Assessments

With the exception of prostate cancer subjects in Parts E and F, post-baseline response assessments in this trial are to be performed every 9 weeks (-10 days).

- For q3w subjects: Response assessments will be performed within 10 days of C4D1, C7D1, C10D1, and every three cycles thereafter.
- For q6w subjects: Response assessments will be performed approximately every 1.5 cycles, i.e., mid-Cycle 2, end of Cycle 3, mid-Cycle 5, end of Cycle 6, etc.

For prostate cancer subjects in E and F, post-baseline response assessments and a bone scan will be performed every 12 weeks (-10 days), i.e., within 10 days of C3D1, C5D1, C7D1, and every two cycles thereafter.

The imaging interval may be increased to every 12 weeks with a +/- 3 week window for subjects who remain on study treatment for ≥ 24 months

7.3. Assessments for Subjects in Part C After Adding Post-Progression Nivolumab

7.3.1. Cycle X Day 1

The following evaluations and procedures will be performed during this visit (± 3 days):

- Physical examination.
- Vital signs pre-and post-infusion.
- Weight.
- ECOG performance status.
- Pregnancy test for WOCBP.
- 12-lead ECG.
- Laboratory assessments: Chemistry, hematology, coagulation, thyroid function, and urinalysis. Laboratory assessments need not be repeated if they were performed within 72 hours of the Day 1 visit.
- Blood samples for PK.
- Record concomitant medications.
- Adverse events assessment.
- JTX-2011 Administration followed by observation for at least 1 hour.
- Nivolumab or pembrolizumab administration followed by observation for at least 1 hour.

7.3.2. Cycle X Days 22 (q6w Subjects Only)

The following evaluations and procedures will be performed during this visit (± 3 days):

- Physical examination.

- Vital signs pre-and post-infusion.
- Weight.
- ECOG performance status.
- 12-lead ECG.
- Laboratory assessments: Chemistry, hematology, and coagulation.
- Record concomitant medications.
- Adverse events assessment.
- Nivolumab or pembrolizumab administration followed by observation for at least 1 hour.

7.4. End of Treatment (All Parts)

At the end of treatment (within 28 days ± 7 days after last dose of study drug):

- Physical examination.
- Vital signs.
- ECOG performance status.
- 12-lead ECG.
- Laboratory assessments including chemistry, hematology, coagulation, thyroid function, and urinalysis.
- Prostate cancer subjects in Parts E and F only:
  - PSA
- Blood samples for Target Engagement, PK/ADA/NAb (not required for Part C subjects receiving nivolumab or pembrolizumab post-progression).
- CT Scan for response assessment (unless performed within 9 weeks of End of Treatment visit [within 12 weeks for prostate cancer subjects]).
- Record concomitant medications.
- Adverse events assessment.

7.5. Long-Term Follow-up

Long-term follow-up assessments will be done every 12 weeks (± 2 weeks) from the last dose of JTX-2011. All subjects who discontinue study treatment will be followed for:

- Survival: Via telephone or email until a) death, b) withdrawal of consent, c) they are lost to follow-up, d) the Sponsor notifies sites that survival follow-up is no longer required, or e) termination of study by the Sponsor
- Assessment of treatment-related SAEs until resolution to baseline or Grade 0-1.

Subjects discontinuing treatment due to reasons other than documented disease progression will have their tumor assessed (using the same modality that was used during study treatment) every 12 weeks (± 2 weeks) for up to 2 years after the last treatment visit, until a) they start a new therapy for their cancer, b) death, c) withdrawal of consent, d) are lost to follow-up, e) the Sponsor notifies sites that tumor assessment is no longer required during long-term follow-up, or f) termination of study by the Sponsor.

8. DESCRIPTION OF STUDY ASSESSMENTS

8.1. Demographics

The following demographic data will be obtained for each enrolled patient: year of birth, gender, ethnicity, and race.

8.2. Medical History

A detailed medical history will be taken at Screening. Significant relevant Medical History within the past 5 years, including smoking history, will be recorded. Disease related history, including known status of relevant gene aberrations or over-expression or viral status should be included (e.g. BRAF, EGFR, HER2, MSI, Epstein Barr Virus, Human Papilloma Virus)

8.3. Physical Examination

A full physical examination (outlined by institutional guidelines), including weight with height (Screening only), will be performed at Screening and End of Treatment visits by a qualified individual. At all other visits, a targeted physical exam will be performed per institutional guidelines.

8.4. Vital Signs

Measurements of vital signs include blood pressure (BP), temperature (T), heart rate (HR), and respiratory rate (RR), oxygen saturation (SpO_2).

8.5. Weight

The determination of JTX-2011 dose will be based on the subject's weight.

8.6. Eastern Cooperative Oncology Group (ECOG) Performance Status

The ECOG performance status assessment should be assessed according to Section 12.3.

8.7. Response Assessment

The anti-tumor activity of study treatment will be assessed using RECIST v1.1 criteria, modified RECIST for subjects with mesothelioma only {Byrne 2004} and PCWG2 guidelines for subjects with prostate cancer only {Scher 2008} as assessed by study investigators and independent central radiology review. Imaging for efficacy assessments will be performed approximately every 9 weeks with the exception of subjects with prostate cancer who will have imaging assessments every 12 weeks with both CT and bone scans; prostate cancer outcomes to be assessed per the PCWG2 guidelines. The imaging interval may be increased to every 12 weeks with a +/- 3 week window for subjects who remain on study treatment for ≥ 24 months.

Immune-related response criteria (irRC) {Wolchok 2009} will also be assessed by independent central radiology review as well as study investigators where feasible.

8.8. Clinical Laboratory Evaluations

All clinical laboratory assays (e.g. Chemistry, Hematology, Coagulation, Urinalysis, pregnancy testing, and Thyroid function) will be performed at local laboratories according to the laboratory's normal procedures. Results will be reported by Investigators in the eCRF. Abnormal laboratory values which are unexpected and not explained by the subject's clinical condition should be repeated until confirmed, explained, or resolved. Changes starting from the initiation of study drug (e.g. JTX-2011 monotherapy or in combination with nivolumab, ipilimumab or pembrolizumab) exposure will be recorded as an adverse event if clinically significant in the judgement of the Investigator. Clinical Laboratory evaluations are summarized in Table 6.

Table 6: Clinical Laboratory Evaluations

Panel	Parameters
Chemistry	Calcium Chloride Total Protein Potassium Glucose Sodium Blood Urea Nitrogen (BUN) Creatinine AST (SGOT) ALT (SGPT) Alkaline Phosphatase (ALP) Bicarbonate Lactate Dehydrogenase (LDH) Albumin Direct Bilirubin Indirect Bilirubin Total Bilirubin Phosphorus Magnesium Uric Acid
Hematology	Calculated ANC WBC RBC Hemoglobin Hematocrit Platelet count Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Coagulation	Prothrombin Time (PT) International Normalized Ration (INR) Activated Partial Thromboplastin Time (aPTT)

Panel	Parameters
Thyroid Function	Total T3 Free T4 TSH
Urinalysis	Dipstick: pH Glucose Protein Bilirubin Ketones Leukocytes Blood Microscopic (if dipstick is positive): WBC RBC Casts
Other	PSA (for subjects with prostate cancer only)

8.9. Pharmacokinetic (PK) Sampling

Plasma PK for JTX-2011 will be collected in ALL parts this study. (See Section 12.1).

Plasma PK for nivolumab, ipilimumab, and pembrolizumab will be collected in the relevant parts of the study.

Pharmacokinetics of JTX-2011 in Parts A and B will be used to inform initiation of the Safety/PK/PD Expansion Cohorts.

If emerging PK data show that a less frequent sampling schedule is warranted, PK sampling may be reduced without a protocol amendment.

A separate Laboratory Manual detailing the PK sample collection, preparation, storage and shipping process will be provided.

8.10. Biomarkers

Biomarkers assessed in this study are summarized in Table 7.

Table 7: Biomarkers

Biomarker	Sample	Purpose
Pharmacodynamics: • Target Engagement	Blood	Inform dose and schedule decision for expansion cohorts
Safety: • Cytokines • Anti-drug Ab and neutralizing Ab for JTX-2011, nivolumab, and ipilimumab	Blood	Assess potential cytokine induction Anti-drug Ab may affect safety and/or efficacy
Potential predictive biomarkers: • ICOS expression by IHC • PD-L1 IHC	Archival/fresh Archival/Fresh	Stratification, correlation with efficacy Explore correlation with efficacy

Biomarker	Sample	Purpose
• Predefined ICOS RNA signature	Archival/Fresh	Explore correlation with efficacy
• DNA for mutational load and neoantigen pre-treatment	Archival/Fresh	Explore correlation with efficacy
Exploratory: • RNA signature (Nanostring® or RNAseq)	Blood/Archival/Fresh	Identify potential predictive gene signature AND assess JTX-2011 induced changes in gene expression
• Multiplex IHC for Immune cell subsets pre-and post-treatment	Fresh biopsy	Assess changes in T cell infiltrate in tumors after treatment
• Immunophenotyping	Blood	Assess effect on peripheral T cells

Please refer to the separate Laboratory Manual detailing the pharmacodynamics sample collection times, preparation, storage and shipping process.

ICOS target engagement (TE), a pharmacodynamic biomarker, will be collected and used to determine RP2D and schedule.

JTX-2011 is not expected to induce changes in inflammatory cytokines (safety) or peripheral immune cells (exploratory), but both measures will be assessed. Anti-drug antibodies to either JTX-2011, nivolumab, ipilimumab, or pembrolizumab may impact efficacy and/or safety, and will be measured throughout the study.

Archival tumor tissue samples will be assessed for expression of ICOS and PD-L1 as potential predictive markers of response to JTX-2011 monotherapy and in combination with nivolumab, ipilimumab, or pembrolizumab, which will be correlated with efficacy outcomes. Potential predictive biomarkers in both archival and fresh tumor specimens, including but not limited to protein assays such as ICOS IHC, RNA assays such as but not limited to predefined ICOS gene signature, novel gene signature as measured by assays such as but not limited to Nanostring®, and DNA based assays of mutational burden, will be assessed at baseline and correlated with efficacy outcomes, if sufficient samples are available. Potential predictive biomarkers in peripheral blood, including RNA profiling and DNA based assays of mutational burden, will be assessed at baseline and correlated with efficacy outcomes, if sufficient samples are available. Paired pre-and post-treatment biopsies will be analyzed for changes in immune cell related gene signatures and immune cell infiltrates, specimens permitting. These will assess the effect of different doses of JTX-2011 on intratumoral immune cell changes that are expected to correlate with efficacy, in order to inform the best dose for continued clinical development.

If emerging pharmacodynamic data show that a less frequent sampling schedule is warranted, biomarker sampling may be reduced without a protocol amendment.

8.10.1. Collection of Biopsies

8.10.1.1. Archival Tissue Collection

As described above, multiple markers will be reviewed in archival tissue. All subjects enrolled in this trial are required to submit archival tumor tissue samples, unless archival material is unavailable (e.g., all tumor blocks are exhausted). These samples will be assessed for expression of ICOS and PD-L1 as potential predictive markers of response to JTX-2011 monotherapy and in combination with nivolumab, ipilimumab, or pembrolizumab, which will be correlated with efficacy outcomes. If sufficient sample is available, additional testing will be performed. In documented cases where archival material is not available, if agreed between the Investigator and Sponsor, the subject may have a fresh biopsy performed to serve as archival tissue (Section 7.1).

8.10.1.2. Fresh Biopsy Collection

As described above, multiple markers will be reviewed in fresh tissue. All subjects enrolled to Parts C, D, F, G, and H will require a pre-treatment fresh biopsy. Subjects enrolled to Parts C and F will also require a fresh biopsy post-treatment with JTX-2011. If, in the opinion of the investigator, a subject does not have a tumor lesion that can be biopsied at acceptable risk, exceptions may be made by obtaining approval from the Sponsor and Medical Monitor.

Upon confirmed progression, an optional fresh biopsy may be collected at the discretion of the investigator for further analysis.

8.10.2. Retention of Samples

If allowable by local guidelines and/or policies, all blood, PBMCs, and tumor tissue samples will be retained for potential additional testing at a later date or to enable development of a companion diagnostic that would help to identify subjects most likely to benefit from JTX-2011 in the future.

Samples will be retained at a secure storage facility (to be selected, qualified, and contracted by Jounce Therapeutics) in case there is need for retesting. At the end of ten (10) years (or some other period based on local guidelines and/or policies), or if Jounce no longer requires the samples, they will be destroyed. Analyses may be conducted by Jounce Therapeutics, Inc. or by a designated lab at their discretion.

Biospecimens will not be labeled with any personal identifiers (e.g., date of birth, initials). They will be labeled with the subject's study number to allow for future exploratory research analyses to be correlated to the study data and treatment/dose assignments.

8.11. 12-Lead ECG

ECGs will be analyzed locally and data must be reported in the eCRF.

8.12. Urinalysis

A dipstick urinalysis will be performed at Screening, Cycle 1 Day 1, and Day 1 of each additional cycle. Urinalysis testing to include: glucose, blood, protein, bilirubin, ketones, leukocytes and pH. If the dipstick is abnormal a microscopic evaluation will be performed.

8.13. Pregnancy Test

A serum pregnancy test must be performed on all women of child-bearing potential (WOCBP) during the Screening Period and prior to every dose of study drug.

8.14. Adverse Events and Serious Adverse Events

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE) as provided in this protocol.

8.14.1. Definition of an Adverse Event (AE)

An AE is any untoward medical occurrence in a 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 clinically significant abnormal laboratory finding), symptom, disease, or exacerbation of a pre-existing condition temporally associated with the use of study drug, whether or not related to the study drug.

Disease progression should not be recorded as an AE/SAE. New or increasing symptoms related to disease progression should be reported as an AE or AEs. When possible, the primary diagnosis of the event meeting SAE criteria should be recorded as the AE/SAE term. (For instance, if a patient is hospitalized for shortness of breath and it is confirmed that this is a symptom of a malignant pleural effusion, then malignant pleural effusion should be reported as the event term, rather than disease progression).

8.14.2. Observation and Recording of AEs

The subject will be required to report any AE that occurs after the main informed consent is signed. SAEs will be reported as outlined in Section 8.16 and recorded in the AE CRF. AEs or SAEs occurring after a subject signs the pre-screening ICF will not be collected.

Study personnel will assess AEs at every visit. The date of onset and resolution (if applicable) of the AE will be documented in the source documents and on the appropriate CRF page. The Investigator will monitor all AEs to the final visit or to a satisfactory resolution if the AE is ongoing.

All AEs will be recorded from the time of signed informed consent until the End of Treatment visit (28 days ± 7 days after the last dose of JTX-2011, nivolumab, ipilimumab, or pembrolizumab, whichever occurred last), and are to be recorded on the appropriate AE pages in the eCRF and in source documents. AEs for the End of Treatment visit may be collected by a telephone contact if the patient is not able to attend an on-site End of Treatment visit. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made then each symptom should be listed individually.

All study drug related AEs/serious adverse events (SAEs) (see Section 8.16 for definition) will be followed to resolution (the subject's health has returned to his/her baseline status or all variables have returned to normal), or until new therapy initiated. Where appropriate, medical tests and examinations will be performed to document resolution of the event(s).

SAE Reporting Contact Information

[redacted]
Tel: [redacted]
Fax: [redacted]
Email: [redacted]

8.14.3. Grading and Severity

Grade refers to the severity of the AE/SAE. Severity will be assessed in this study using the NCI CTCAE, version 4.03 (see Section 12.2.1).

In the event that an AE is not covered by the CTCAE, the assessment of severity will be determined by using the CTCAE general guideline:

Table 8: Grading for Events Not Covered By the CTCAE

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The Investigator will evaluate all AEs as to their severity.

- An AE that is assessed as severe should not be confused with an SAE. Severity is a category used for rating the intensity of an event; both AEs and SAEs can be assessed as severe. An event is described as 'serious' when it meets one of the pre-defined outcomes as described in Section 8.14.5

Worsening of a pre-treatment event, after initiation of JTX-2011 alone or in combination with nivolumab, ipilimumab or pembrolizumab must be recorded as a new AE.

8.14.4. Relationship Categorization

An Investigator qualified in medicine must make the determination of relationship to study drug for each AE/SAE. The Investigator should decide whether, in his or her medical judgment there is a reasonable possibility that the event may have been caused by the study drug. If no valid reason exists for suggesting a relationship, the AE/SAE should be classified as "definitely not". If there is a valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the study drug and the occurrence of the AE/SAE, the AE/SAE

should be considered "possibly related". Table 9 should be used for guidance in the determination of relationship:

Table 9: Guidance in Determining the Relationship of an Adverse Event

Term	*Relationship*	*Definition*
Unrelated	No	There is no association between study drug and the reported event.
Possible	Yes	The event follows a reasonable temporal sequence from the time of study drug administration and/or follows a known response pattern to the study drug, but could also have been produced by other factors.
Probably Related	Yes	A definite causal relationship exists between study drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event.

If the causal relationship between an AE/SAE and JTX-2011 alone or in combination with nivolumab, ipilimumab, or pembrolizumab is determined to be possible or related, the event will be considered to be related to JTX-2011 for the purposes of expedited regulatory reporting.

8.14.5. Outcome Categorization

Outcome of an AE/SAE may be classified as resolved, resolved with sequelae, unresolved, or fatal. Death is an outcome of an event. The event that resulted in death must be recorded on the appropriate CRF.

8.14.6. Clinical Laboratory Evaluations

A clinical laboratory AE is any laboratory value that is considered clinically significant by the Investigator and has caused a medical intervention or accompanied by clinical symptoms. Laboratory abnormalities that have not required medical intervention should not be recorded as AEs and will be captured and reported in the Laboratory section of the clinical study report. If a medical intervention occurs, it should be recorded as a treatment with the abnormal laboratory finding as the AE.

The Investigator should decide, based upon the AE criteria and the clinical condition of the patient, whether a change in a laboratory parameter is clinically significant and therefore represents an AE.

8.15. Pregnancy

Pregnancy will not be considered a serious adverse event. [redacted]

If the outcome of the pregnancy meets serious criteria (miscarriage or congenital anomaly/birth defect), it should be reported as an SAE.

The pregnant female study participant must be withdrawn from the study. Every effort should be made to gather information regarding the pregnancy outcome until 8 weeks post-partum. It is the responsibility of the Investigator to obtain all pregnancy information.

8.16. Serious Adverse Event Reporting

8.16.1. Definition of a Serious Adverse Event (SAE)

A Serious Adverse Event is any untoward medical occurrence (whether considered to be related to study drug or not, except for those events described in Section 8.16.3) that at any dose:

- Results in death;
- Is life-threatening (the term "life-threatening" in the definition of "serious" refers to an event which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- Requires inpatient hospitalization (at least 24 hours inpatient) or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital abnormality/birth defect.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above as these events may be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

8.16.2. SAE Classifications

Elective or previously scheduled hospitalizations for pre-existing conditions which have not worsened after initiation of treatment should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE.

8.16.3. Protocol-Specified Expected Events

Patients with advanced solid malignancies are at risk for many adverse events as a consequence of prior therapy and as a result of their disease.

Subjects receiving immune therapies are at risk for immune-related AEs. IrAEs are typically responsive to interruption or discontinuation of the immunotherapy in combination with immunosuppressive drugs such as steroids or occasionally tumor necrosis factor-blocking antibodies. At present, there is no clear preventive strategy to avoid irAEs {Michot 2016}.

These events that are expected due to the subject's disease or "immune-related" events that are expected with immunostimulatory therapy must be reported in the clinical database:

- Disease-related adverse events may include:

- Fatigue;
- Bone, joint, or muscle pain;
- Disease progression;
- Death due to disease progression;
- Cough in subjects with lung cancer;
- Dysphagia or odynophagia in subjects with head and neck cancer;
- Abdominal pain in subjects with gastric cancer.
- General therapy-related events may include:
  - Catheter-related events.
- Immune-related adverse events (well documented and expected with nivolumab, ipilimumab, and pembrolizumab, and expected with JTX-2011) may include:
  - Dermatitis;
  - Pneumonitis;
  - Hepatitis;
  - Enterocolitis;
  - Hypophysitis;
  - Adrenal insufficiency;
  - Thyroid dysfunction;
  - Nephritis;
  - Infusion reaction;
  - Rash;
  - Pruritus;
  - Vitiligo.

The occurrence of these expected events will be monitored by Jounce and may be submitted to health authorities in either an expedited or non-expedited manner, as appropriate.

8.16.4. Observation and Recording of SAEs

All SAEs must be reported to Novella within 24 hours of first awareness of the event.

Additional follow-up information, if required, or available, should be recorded on a follow-up SAE Report Form and faxed to Novella Drug Safety within one business day of discovery by site.

All SAEs, whether related or unrelated to study drug, will be recorded from the time of signed informed consent until resolution or new therapy initiated or for 28 days post final dose if no new therapy is initiated. Any SAEs considered to have at least a possible relationship to the study drug and discovered by the Investigator at any time period after the subject's study treatment has ended should be reported according to the timeframe described above.

Study drug-related SAEs will be followed until resolution, stabilization or subject receives new therapy.

At a minimum, the site number, Investigator's name, subject number, event name, the date of onset, a short description of the event and the Investigator's preliminary assessment of causality must be provided at the time of the initial SAE report.

The onset date of the SAE is defined as the onset date of signs and symptoms or a change in baseline when the SAE met seriousness criteria.

The resolution date of the SAE is defined as the date in which the criteria of seriousness is no longer applicable (e.g., discharge from hospitalization).

All SAEs that are ongoing events at the time of death should be considered not resolved at time of death.

The Investigator is encouraged to discuss with the Medical Monitor any SAEs for which the issue of reportability is unclear or in question.

The Investigator must review, sign, and date the SAE Report Form to confirm the accuracy of the information recorded on the SAE Report Form along with the corresponding source documentation.

8.17. Regulatory Authorities and IRBs

Jounce or its designee is responsible for notifying the investigational sites and all heath authorities (e.g. FDA) of all expedited SAEs.

The Investigator will notify his or her IRB of serious, related and unexpected AE(s) or significant risks to subjects. The Investigator must keep copies of all AE information, including correspondence with Jounce or Local Ethics Committees on file.

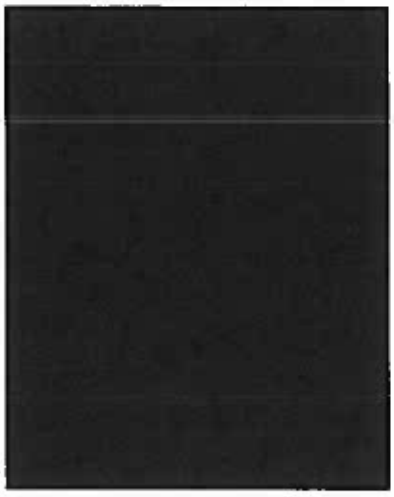
It is the responsibility of the Principal Investigator (PI) to notify the IRB of all SAEs that occur at his or her site as per site guidelines. Investigators will be notified of all suspected, unexpected SAEs (7/15 Day Safety Reports) that occur during any clinical studies that are using the investigative compound. Each site is responsible for notifying its IRB/EC of these additional SAEs.

8.18. Drug Safety Contact Information

[redacted]

Medical Monitor for North America:

[redacted]



9. STATISTICAL ANALYSES

9.1. Endpoints

The following endpoints will be used to measure the efficacy, safety, and exploratory objectives of the study.

9.1.1. Safety Endpoints

The following safety endpoints will be assessed:

- Incidence and severity of treatment-emergent adverse events;
- Incidence and severity of treatment-emergent changes in clinical laboratory values;
- Incidence of dose limiting toxicities;
- Incidence of anti-drug antibodies to JTX-2011 and/or nivolumab, ipilimumab, or pembrolizumab;
- Incidence of neutralizing antibodies to JTX-2011 and/or nivolumab, ipilimumab, or pembrolizumab;
- Incidence of decreases in ECOG performance status;
- Incidence of clinically significant changes in ECG measurements.

9.1.2. Efficacy Endpoints

Efficacy will be evaluated using RECIST v1.1 (Section 12.4) and immune-related Response Criteria (irRC) (Section 12.7), or for modified RECIST only for subjects with mesothelioma (Section 8.7) with the following endpoints:

- Overall Response Rate: % of subjects with Complete Response (CR) plus Partial Response (PR);
- Duration of Response in months;
- Disease Control Rate: % of subjects with Complete Response + Partial Response + Stable Disease;
- Landmark Progression Free Survival Rate at 6 months and 12 months;
- Progression Free Survival.
- Landmark Overall Survival at 6 months and 12 months;
- Overall Survival.

9.1.3. Pharmacokinetic Endpoints

PK endpoints are for JTX-2011 unless otherwise specified. The following PK endpoints will be determined (if feasible):

- Maximum observed concentration (C_{max}) of JTX-2011, nivolumab, ipilimumab and/or pembrolizumab in serum for all treatment cycles);
- Minimum measured concentration (C_{min})of JTX-2011, nivolumab and/or pembrolizumab in serum for treatment cycles >1);
- Time from dosing to maximum measured concentration (t_{max});
- Area under the serum concentration-time curve over the dosing interval ($AUC_{0-\tau}$)

- Area under the serum concentration-time curve over the time interval from 0 to 336 hours after dosing (AUC_{0-336}) for nivolumab, in order to compare nivolumab PK to PK in literature in which nivolumab is dosed q2w);
- Area under the concentration-time curve of from time 0 extrapolated to infinity ($AUC_{0-\infty}$) JTX-2011, nivolumab, ipilimumab and/or pembrolizumab in serum over the time interval from 0 extrapolated to infinity);
- Percentage of $AUC_{0-\infty}$ obtained by extrapolation from the last evaluable time point ($\%AUC_{tz-\infty}$);
- Terminal rate constant in serum (λ_z);
- Terminal half-life of JTX-2011 or nivolumab in serum ($t_{½}$);
- Mean residence time (MRT_{iv}) of JTX-2011, nivolumab, ipilimumab and/or pembrolizumab in the body after intravenous infusion);
- Total clearance (CL)of the analyte in serum after intravenous infusion;
- Apparent volume of distribution (V_z) during the terminal phase λ following intravenous infusion;
- Apparent volume of distribution at steady state following intravenous infusion (V_{ss}).
- Assess impact of ADA on PK

9.1.4. Pharmacodynamics Endpoints

The following pharmacodynamics endpoints will be determined (if feasible):

- Percent target engagement at each time point of pharmacodynamics marker measurement;
- Maximum % target engagement in serum (E_{max}) and minimum % target engagement in serum (E_{min});
- Area under the effect-time curve of the pharmacodynamics marker in serum over the time interval from t1 to t2 ($AUEC_{t1-t2}$), where t2 is 8 days, 15 days, and 21 days after the first dose of JTX-2011).

9.2. Exploratory Endpoints

9.2.1. Safety

The following safety exploratory endpoints will be assessed (if feasible):

- Incidence and severity of increase in inflammatory cytokines;
- Change in peripheral blood lymphocyte subsets.

9.2.2. Predictive

Efficacy endpoints will be assessed for correlation with the following exploratory predictive biomarkers, if samples are available:

- ICOS IHC score;
- Predefined ICOS RNA signature;
- Exploratory RNA signature;
- DNA mutational load;
- Neoantigen expression;

- PD-L1 IHC score.

9.2.3. Mechanistic

The following mechanistic exploratory endpoints will be assessed (if feasible):

- Change in peripheral blood immune cell gene signatures;
- Change in intratumoral immune cell gene signatures;
- Change in intratumoral immune cell subsets.

9.3. Statistical Basis for Sample Size

Approximately 380 evaluable subjects will be enrolled in 4 parts of the study.

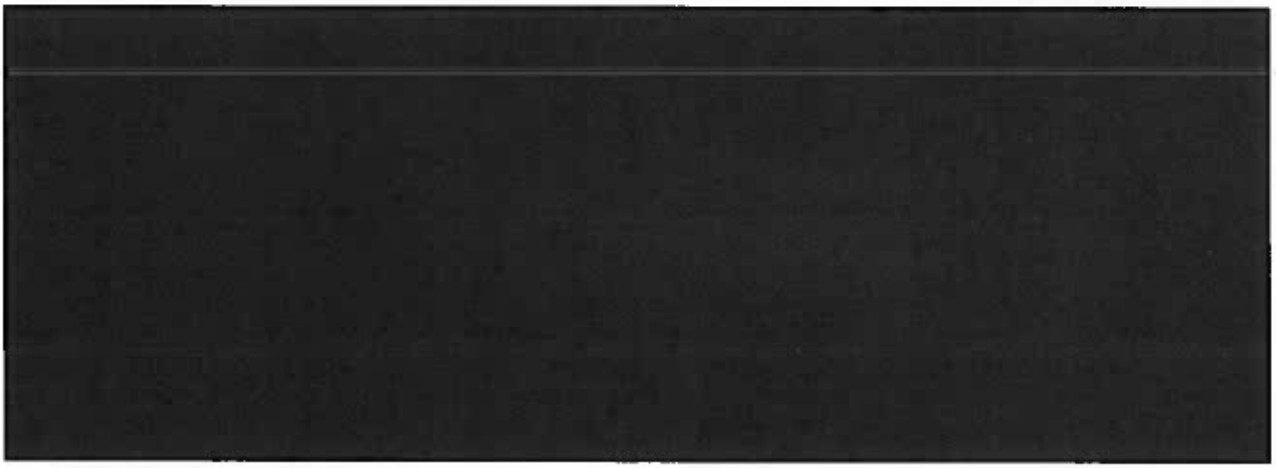
For **Part A, Part B, Part E,** and **Part G,** the choice of the number of subjects was based on the classical 3 + 3 design. The approximate sample size in the dose escalation cohorts in Part A will be 36 evaluable subjects assuming that 6 subjects are assigned at each of 6 planned dose levels. The approximate sample size of the dose escalation cohorts in Part B will be 24 evaluable subjects assuming that 6 subjects are assigned at each of 4 planned dose levels. The approximate sample size of the dose escalation cohorts in Part E will be 18 evaluable subjects assuming that 6 subjects are assigned at each of 3 planned escalation dose levels. The approximate sample size of the dose escalation cohorts in Part G will be 12 evaluable subjects assuming that 6 subjects are assigned at each of 2 planned dose levels. The dose escalation will stop at the dose level at which 2 subjects experience any of the defined DLTs, which would avoid selecting a dose level with > 33% chance of observing a DLT into further development.

Approximately 8 subjects are planned to be added to each of 2 (or more) dose levels in Parts A (AP1, AP2) and B (BP1, BP2) where 70% target engagement is observed in 2/3 subjects at either Day 8 or Day 21 (see Section 6.4), to obtain additional safety and PK/PD data. This addition will yield a total of 11 (or 14) subjects on the same dose level, providing at least 70% chance to observe 4 or more targeted toxicities if the true toxicity rate is 0.3 or more for the dose.

Subjects may also be added if the exploration of intermediate dose level(s) of JTX-2011 is warranted or if the SMC recommends adding additional subjects at a given dose level to further understand and clarify safety issues.

In **Part C, Part D, Part F and Part H** the preliminary efficacy signal, measured by the overall response rate (ORR), will be evaluated using a group sequential design with 1 interim look for futility. The following hypotheses H_0: ORR ≤ 0.08 versus H_1: ORR ≥ 0.20 will be tested with a 90% power at a 2-sided α=5%. As the first step, 15 (Part C) or 15 (Part D) or 15 (Part F) or 15 (Part H) subjects will be enrolled for each cohort in the current protocol. The anticipated total sample size for each cohort could be as large as 76 if warranted by the result obtained from the first 20 or 15 subjects. The following table lays out different scenarios based on the observed ORR from the first 20 or 15 subjects within each cohort:

Table 10: Operating Features of A Group Sequential Design with 1 Futility Interim Look at 20 or 15 Subjects with 90% Power and 2-sided α=5%.



9.4. Statistical Analysis

A high-level summary of major statistical analyses for the data collected through this protocol is included in this section. Details of planned statistical analyses and data presentations for safety and efficacy data will be specified in the Statistical Analysis Plan (SAP). Analysis of predictive biomarkers will be specified in the exploratory analysis plan (EAP). Jounce Biostatistics and Programming or designated clinical research organization (CRO) will perform the statistical analysis of the related data (SAP and EAP); SAS (Version 9.4, or higher) will be used to generate all statistical outputs (tables, figures, listings, and datasets). Analysis of other data (data other than safety or efficacy data) will be specified in the individual stand-alone analysis plans. All plans will be finalized and approved prior to the clinical database lock achieved for this study.

9.4.1. Determination of Sample Size

For Part A, Part B, Part E, and Part G, the choice of the number of subjects is based on the classical 3 + 3 design. The approximate sample size in the dose escalation cohorts in Part A will be 36 evaluable subjects assuming that 6 subjects are assigned at each of 6 planned dose levels. The approximate sample size of the dose escalation cohorts in Part B will be 24 evaluable subjects assuming that 6 subjects are assigned at each of 4 planned dose levels. The approximate sample size of the dose escalation cohorts in Part E will be 18 evaluable subjects assuming that 6 subjects are assigned at each of 3 planned dose levels. The approximate sample size of the dose escalation cohorts in Part G will be 12 evaluable subjects assuming that 6 subjects are assigned at each of 2 planned dose levels.

Approximately 8 additional subjects will be enrolled in safety/PK/PD expansion cohorts at each of 2 or more dose levels in Parts A (AP1, AP2) and B (BP1, BP2) to obtain additional safety and PK/PD data. Subjects may also be added if exploration of intermediate dose level(s) of JTX-2011 is warranted or if the SMC recommends adding additional subjects at a given dose level to further understand and clarify safety issues.

Approximately 120 subjects may be enrolled in Part C (approximately 15 in each cohort). Approximately 90 subjects may be enrolled in Part D (approximately 15 subjects per cohort). Approximately 30 subjects may be enrolled in Part F (approximately 15 subjects per cohort). Approximately 15 subjects may be enrolled in each Part H (assuming 3-6 will be enrolled in Part G). For Part C, Part D, Part F, and Part H, a group sequential design will be used to evaluate the preliminary efficacy of JTX-2011 or JTX-2011 in combination with nivolumab, ipilimumab or pembrolizumab, with an interim look for futility. [redacted]

9.4.2. Analysis Set

All Subjects Set will include all subjects who have signed the informed consent and have subject numbers in the electronic clinical database.

The **Safety Population (SAF)** will include all subjects who have been treated with at least one dose of study drug (JTX-2011, nivolumab, ipilimumab, or pembrolizumab). The SAF will be the primary analysis set for all efficacy and safety analyses, unless otherwise specified.

Pharmacokinetic/Pharmacodynamic Analysis Set (PK/PD Set) will include all subjects who received at least one dose of the study drug and who provide at least one observation for at least one of the PK or PD endpoints without protocol violations that would be deemed by the trial pharmacokineticist to interfere with the PK or PD analysis.

Immunogenicity Analysis Set will include all subjects who received at least one dose of the study drug and provided one serum sample that could be successfully analyzed by both a screening and confirmatory validated ADA assay (for ADA analysis) or NAb assay (for NAb analysis).

9.4.3. General Considerations

All individual subject data for those who signed ICF and obtained subject numbers will be presented in data listings.

Unless otherwise specified, continuous endpoints will be presented by number of non-missing values, mean, median, standard deviation, minimum, and maximum values. Categorical endpoints will be presented by frequencies and percentages.

9.4.4. Patient Disposition

The number of subjects in each defined analysis set will be summarized. In the same summary table, subjects who completed study, or discontinued study early will be summarized with reasons for subjects' withdrawal (from treatment or follow-up) by frequencies and percentages.

9.4.5. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized based on SAF. Continuous endpoints will be summarized by N, mean, median, minimum, maximum, and standard deviation. Categorical endpoints (includes binary endpoints) will be summarized by frequencies and percentages per category.

9.4.6. Concomitant Medication

Medications used in this study will be coded by using the World Health Organization Drug Dictionary Enhanced (WHO-DDE) and categorized as the following:

- **Prior medication:** any medication that started before the first dose of study drug, regardless of when the medication ended.
- **Concomitant medication:** medication continued or newly received at or after the first dose of study drug through the end of treatment emergent period (defined in the SAP).
- **Post-treatment medication:** medication continued or newly received after the treatment emergent period.

A given medication can be classified as a prior, a concomitant, or a post-treatment medication; both prior and concomitant; both concomitant and post-treatment; or prior, concomitant, and post-treatment. If a medication has a missing or partially missing start/end date and it cannot be determined whether it was taken before the first dose, concomitantly, or beyond the treatment emergent period, it will be considered as prior, concomitant, and post-treatment.

For the SAF, prior medications and concomitant medications will be summarized descriptively by: 1) preferred name; and 2) anatomic class (ATC) level 1, ATC level 2, and preferred name. Post-treatment medications will be listed by subject.

9.4.7. Subject Adherence

For subjects in SAF, number of treatment cycles per patient will be summarized by frequencies and percentage of subjects who received each number of treatment cycles.

9.4.8. Safety Analyses

Assessment of safety will be performed for all subjects who receive at least one dose of study drug and for whom at least one post-dose safety observation is recorded (the Safety Population). Safety data that will be evaluated include DLTs, AEs/SAEs (including changes from baseline in physical examination findings), clinical laboratory results, vital signs, ECOG performance status, ECGs and any other pertinent results. Safety and tolerability endpoints will be summarized descriptively.

9.4.8.1. Adverse Events

Adverse events will be classified into standardized terminology from the verbatim description (Investigator term) according to the most recent version of the MedDRA adverse event coding dictionary at time of data analysis. Adverse events will be presented by Preferred Term nested within System Organ Class (SOC). Verbatim description and Preferred Term and SOC MedDRA-level terms for all AEs will be contained in the data listings of the Clinical Study Report for this protocol.

Adverse events will be summarized by the incidence of AEs/SAEs by body system and by preferred term. The incidence of AEs/SAEs will be based on the numbers and percentages of subjects with AEs/SAEs. Although a MedDRA term may be reported more than once for a patient, that patient will be counted only once in the incidence count for that MedDRA term. The severity of the AEs/SAEs and the relationship to the study drug will be summarized for each body system and preferred term by treatment group. Withdrawals due to AEs/SAEs will be summarized for each body system and preferred term.

AEs/SAEs will be classified based on the AE start date in relation to the first dose date as the following:

- Treatment-emergent AEs, defined as AEs that newly emerge, re-emerge or worsen on or after the first dose of study drug; all these AEs would have a start date on or after the first dose date of the study drug.
- Pre-treatment events, defined as AEs that newly emerge, re-emerge or worsen before the first dose of study drug; all these AEs would have a start date before the first dose date of the study drug.
- Post-treatment events, defined as AEs that newly emerge, re-emerge or worsen after the treatment emergent period (defined in SAP) of the study drug; all these AEs would have a start date after the last day of the safety window of the study drug.

Only treatment emergent AEs will be summarized. All adverse events will be included in all AE data listings with flags indicating treatment emergent, pre- or post-treatment.

In consideration of the varying durations of treatments, the incidence of treatment emergent adverse event will be presented in the following ways, as appropriate, (1) by cohort and overall; (2) by time interval, depending on the distribution of duration of treatment, e.g., by 1-, 3-, 6-, or 12-month intervals from start of therapy; and (3) by event rate per patient year (i.e., # of events per patient per year).

9.4.8.2. Clinical Laboratory Evaluation

Clinical laboratory values will be evaluated for each laboratory parameter by subject. Abnormal laboratory values will be identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be included in the Clinical Study Report for this protocol.

Descriptive summary statistics (mean, standard deviation, median and range) of the laboratory parameters will be evaluated for hematology and biochemistry. Categorical values will be summarized using number of observations and percentages (urinalysis assessment).

Laboratory test results will be assigned an LNH classification according to whether the value was below (L), within (N), or above (H) the laboratory reference range. Summary data of LNH will be provided by the worst category and by the shift from baseline to the worst. In addition, the CTCAE grading system will be implemented to safety laboratory values. The resulted grades of laboratory assessments will be summarized as categorical data.

Clinical laboratory results will also be evaluated using outlier criteria (potentially clinically important per investigator's discretion). For the incidence of outliers, each patient will be counted only once in the laboratory parameter value high and low categories, as applicable.

9.4.8.3. Vital Signs

Vital sign values (BP, T, HR, RR, and SpO_2), and weight will be evaluated on an individual basis by patient. Abnormal vital sign values will be identified as those outside (above or below) the reference range. Descriptive summary statistics (mean, standard deviation, median, and range) for vital sign parameters will be tabulated.

9.5. Efficacy Analyses

For Parts C, D, F, and H, the rate of overall response (CR + PR), rate of disease control (CR+PR+SD), as well as rate of complete response, partial response, or stable disease will be summarized by frequencies and percentages for each cohort. The duration of response measured by the number of months from first confirmed CR/PR to disease progression will also be provided by cohort. The evaluation of the response will be based on RECIST v1.1 criteria and immune-related response criteria, respectively.

Time-to-progression free survival and overall survival will be estimated by Kaplan-Meier method. The median time to event will be presented with 25%- and 75%-quantiles.

More details of safety and efficacy analyses will be specified in SAP including the efficacy analyses for cohorts in Part A and B where efficacy is an exploratory endpoint.

As part of the exploratory objectives, the correlation between efficacy and potential predictive biomarkers will be evaluated to generate hypotheses for further testing and the details will be specified in EAP.

9.5.1. Interim Analyses

This is an open-label study. No formal interim analyses are planned within the current protocol. However, if the number of responses in any cohort of Parts C, D, or F is more than the prespecified futility boundary based on the group sequential design (Section 9.3), the study may enroll additional subjects for a more robust determination of efficacy.

9.5.2. Changes to the Planned Statistical Methods

Changes to the planned statistical methods will be documented in the clinical study report.

9.5.3. Pharmacokinetic Analyses

Pharmacokinetic parameters following the first dose will be calculated by non-compartmental analysis using validated software such as Phoenix WinNonLin v. 6.3 (Certara, Inc.). C_{max} and C_{min} values from subsequent doses will also be tabulated and reported. Only concentration values within the validated concentration range and actual sampling times will be used for the calculation of pharmacokinetic parameters. Concentrations used in the pharmacokinetic calculations will be in the same format provided in the bioanalytical report, (that is, to the same number of decimal places provided in the bioanalytical report).

If any pre-first dose value is greater than 5% of C_{max}, the subject's pharmacokinetic data will be not included in any statistical evaluations. The individual pharmacokinetic parameters of such a subject will be calculated and listed separately. If a pre-first dose concentration is above the lower limit of assay quantitation, but less than or equal to 5% of the subject's C_{max} value, the

subject's data will be included without any adjustments in all pharmacokinetic measurements and calculations.

Every effort will be made to include all concentration data in an analysis. If not possible, a case-by-case decision will be used to determine whether the value should only be excluded from half-life estimation or the complete analysis. If a concentration is only excluded from half-life determination, it will be used for all other calculations (e.g. descriptive statistics) and for graphical presentation.

The following descriptive statistics will be calculated for serum concentrations as well as for all pharmacokinetic parameters: N, arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation. The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations.

In tabulation of PK or PD data, scheduled samples that could not be obtained or analyzed, or samples from which concentration data was identified by the bioanalytical lab as below the limit of quantitation (BLQ) will be ignored and not replaced by zero at any time point except the pre-first dose baseline for PK. Descriptive statistics of concentrations or biomarkers at specific time points will be calculated only when at least ½ of the individuals have concentrations or biomarker data within validated ranges. The overall sample size to decide whether the "½ rule" is fulfilled will be based on the total number of samples intended to be drawn for that time point.

Dose proportionality of the pharmacokinetic endpoints $AUC_{0\text{-}tz}$, $AUC_{0\text{-}\infty}$, and $_{ma}$ will be explored based on a standard regression model. Based on the estimate for the slope parameter β, a two-sided- 95% confidence interval for the slope will be computed. The assumption of a linear relationship between the log-transformed pharmacokinetic endpoint and the log-transformed dose will be checked. Perfect dose proportionality would correspond to a slope of 1.

If dose proportionality over the entire dose range investigated cannot be shown, an attempt will be made to identify dose range(s) where dose proportionality can be assumed.

Attainment of steady state will be explored by pairwise comparison of the trough concentrations of JTX-2011 measured at the beginning of each treatment cycle. If trough concentrations cannot be reported because they are BLQ, attainment of steady state will be assessed from a population PK model.

9.5.4. Pharmacodynamics Analyses

Graphical representations of dependence of % receptor occupancy on serum JTX-2011 concentrations will be used to explore a PK/PD relationship. If a relationship is apparent, the data will be used to attempt to fit the data to a suitable PK/PD model (e.g., E_{max} model). Curve fitting will be done with appropriate software, e.g., Phoenix WinNonLin v. 6.3.

10. DATA QUALITY ASSURANCE

This study will be organized, performed, and reported in compliance with Jounce /CRO's Standard Operating Procedures, protocols and working practice documents, and the requirements of ICH/GCP guidelines. Compliance will be achieved through a combination of study specific audits of investigative sites and audits at regular intervals of the Jounce /CRO's systems for data handling, analysis, and reporting.

10.1. Data Collection

Investigators or designees will enter the information required by the protocol onto the eCRFs. Each investigative site will be visited as frequently as documented in the monitoring plan by the CRO on behalf of Jounce to review the eCRFs for completeness and accuracy. The CRO representative will highlight any discrepancies found between source documents and the completed eCRFs and ensure that appropriate site personnel address the discrepancies. When a discrepancy results in corrected eCRF data, the correction will be reviewed again against the correct source documentation. Uniform procedures will be discussed at the Site Initiation Visit.

10.2. Clinical Data Management

Data from eCRFs and other external data will be entered into a clinical database as specified in the CRO's data management plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database.

Data from eCRFs and other external data will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. Only authorized personnel will make corrections to the eCRF and all corrections will be documented in an audit trail.

11. ADMINISTRATIVE PROCEDURES

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that Jounce and Investigators abide by Good Clinical Practice (GCP) as described in the ICH Harmonised Tripartite Guideline E6: GCP: Consolidated Guideline, and 21 CFR Parts 50, 54, 56, and 312. Compliance with these regulations also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki. The study will also be carried out in keeping with local legal and regulatory requirements.

11.1. Institutional Review Board (IRB)

It is the responsibility of the Investigator to submit this protocol, the informed consent document (approved by Jounce or its designate), relevant supporting information and all types of patient recruitment information to the IRB for review, and all must be approved prior to site initiation. Prior to implementing changes in the study, Jounce and the IRB must also approve any revised informed consent documents and amendments to the protocol.

On the approval letter, the study reference, the date of review and actions taken should be clearly stated. Investigational Product will not be released and the patient recruitment will not begin until this written approval has been received by Jounce or its designee.

The Investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol. The Investigator must also keep the IRB informed of any serious and significant AEs.

11.2. Informed Consent

It is the responsibility of the Investigator to obtain written Informed Consent from subjects. All consent documentation must be in accordance with applicable regulations and GCP. Each patient or the patient's legally authorized representative is requested to sign the Patient Informed Consent Form (ICF) after the patient has received and read the written patient information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences and the patient's rights and responsibilities. A copy of the informed consent documentation (consent form or patient information sheet and the consent form, as applicable) must be given to the patient or the patient's legally authorized representative. If applicable, it will be provided in a certified translation of the patient's local language. Signed consent forms must remain in each patient's study file and must be available for verification by study monitors at any time.

Each PI will provide Jounce with a copy of the IRB approved consent forms, and a copy of the IRB's written approval, prior to the start of the study. Additionally, if the IRB required modification of the sample patient information and consent document provided by Jounce, the documentation supporting this requirement must be provided to Jounce.

Jounce reserves the right to delay initiation of the study at a site where the informed consent forms do not meet the standards of applicable regulations and ICH GCP.

11.3. Subject Privacy

Jounce and the Investigator affirm and uphold the principle for the patient's right to protection against invasion of privacy. Throughout this study, all data collected and analyzed by Jounce (or designee) will be identified by an identification number.

To verify compliance with this protocol, Jounce will require that the Investigator permit its monitor to review those portions of the patient's primary medical records that directly concern this study (including but not limited to laboratory test results, ECG reports, and hospital and outpatient records). Should access to such medical records require a waiver or authorization separate from the statement of informed consent, the Investigator will obtain such permission in writing from the patient before the patient is entered into the study.

11.4. Study Monitoring

Monitoring of the study will be performed by a representative of Jounce's CRO. At the monitoring visits, the progress of the study will be discussed with the Investigator, or his/her representative. The ICFs will be reviewed for signatures and the eCRFs checked for completeness and accuracy. Patient source data must be available for review. The Investigator and his/her staff are expected to cooperate with the study monitor and be available during at least a portion of the monitoring visit to review the eCRFs and any queries/resolutions, answer questions, and provide any missing information.

The study monitor will record the date of each visit together with a summary of the status and progress of the study. Proposed actions will be confirmed with the Investigator in writing.

Telephone contact will be made with the Investigator as necessary during the data collection period and during the data and report writing periods.

11.5. Modification of Protocol

All amendments to the protocol must be documented in writing, reviewed, and approved by the Investigator and Jounce, and submitted to the IRB for approval prior to initiation, except in cases where required for patient safety. If the protocol amendment substantially alters the study design or potential risk to the patient, new written informed consent for continued participation in the study must be obtained from each patient.

11.6. Suspension or Termination of Study

Should conditions requiring further clarification arise before the decision to proceed with or terminate the study can be reached, the study will be suspended until the situation has been resolved.

Jounce has the right to terminate this study and remove all study material from the site at any time. Examples of where this might occur include but are not limited to:

- It becomes apparent that patient enrollment is unsatisfactory with respect to quality and/or quantity or data recording is inaccurate and/or incomplete on a chronic basis;
- The incidence and/or severity of adverse events in this study indicate a potential health hazard caused by treatment with the study medication.

11.7. Departure from Protocol

No deviation may be made from the protocol unless an amendment has been agreed to in writing by both the Investigator and Jounce and approved by the IRB. Investigative sites will contact the medical monitor to request clarifications regarding any aspect of the clinical study or eligibility of subjects. Any study-wide updates may be released via administrative memo from the Sponsor when appropriate.

When an emergency occurs that requires a departure from the protocol for an individual, a departure will be only for that patient. The Investigator or other physician in attendance in such an emergency will, if circumstances and time permit, contact Jounce or their representatives, immediately by telephone. Such contacts will be made as soon as possible to permit a decision as to whether or not the patient (for whom the departure from protocol was affected) is to continue in the study. The source documents will completely describe the departure from the protocol and state the reasons for such departure. In addition, the IRB will be notified in writing of such departure from protocol.

11.8. Recording, Access and Retention of Source Data

The Investigator must permit authorized representatives of Jounce, the regulatory authorities, the IRB, auditors and interested commercial parties to inspect facilities and records relevant to this study. Source data to be reviewed during this study will include, but are not limited to: patient's medical file, original laboratory reports, X-rays/scans, pathology reports, ECGs, etc. All key data must be recorded in the patient's source documents.

The monitor (auditors, IRB or regulatory inspectors) may check the eCRF entries against the source documents. The consent form will include a statement by which the subjects allow the monitor/auditor/inspector from Jounce or its representatives, regulatory authorities or the IRB access to source data which substantiate information recorded in the eCRFs. These personnel, bound by professional secrecy, will not disclose any personal information or personal medication information.

As described in the ICH GCP Guidelines, 'essential documents', including eCRFs, source documents, consent forms, laboratory test results and the investigational product inventory records, should be retained by the Investigator until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with Jounce. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained. The Investigator must obtain written permission from Jounce prior to the destruction of any study document.

These records must be made available at reasonable times for inspection and duplication, if required, by a properly authorized representative of the U.S. Food and Drug Administration (FDA) in accordance with the U.S. Code of Federal Regulations 21 CFR 312.68 or other regulatory authorities in accordance with regulatory requirements.

11.8.1. Case Report Forms

Electronic case report forms (eCRF) will be used for data collection for this study.

The Investigator is responsible for maintaining adequate and accurate source documents from which accurate information will be transcribed into eCRFs which have been designed to capture all observations and other data pertinent to the clinical investigation. eCRFs should be completed by the Investigator or delegate as stated on the Delegation of Authority Log. Overwriting of information or use of liquid correcting fluid is not allowed in the source document.

The eCRFs must be reviewed and electronically signed and dated by the Investigator once all data has been entered and all queries resolved. Once the Study Monitor has verified the contents of the completed eCRF against the source data, queries may be raised if the data are unclear or contradictory. The Investigator must address all queries.

11.9. Good Clinical Practice (GCP) Compliance

The Investigator must undertake to perform the study in accordance with, ICH GCP Guideline E6, local IRB requirements, and 21 CFR.

It is the Investigator's responsibility to ensure that adequate time and appropriate resources are available at the study site prior to commitment to participate in this study. The Investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The Investigator will maintain a list of appropriately qualified persons to whom the Investigator has delegated significant study-related tasks. An up-to-date copy of the curriculum vitae for the Investigator and sub-Investigator(s) will be provided to Jounce (or designee) before starting the study.

If the patient has a primary physician the Investigator should, with the patient's consent, inform them of the patient's participation in the study.

11.9.1. Quality Control and Quality Assurance

A site monitoring plan will be developed to ensure the human patient protection, study procedures, laboratory, study intervention administration, and data collection processes are of high quality and meet Jounce, GCP/ICH, and regulatory guidelines.

The Investigator will permit authorized representatives of Jounce and the respective regulatory authorities to inspect facilities and records relevant to this study if needed.

Initial site training will be provided by Jounce. Training for new staff will be provided by current study nurses and study coordinators under the supervision of the PI. Additional training will be provided by Jounce as needed.

The Data Management Team will implement quality control procedures beginning with the data entry system and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

11.9.2. Publications

All manuscripts, abstracts or other modes of presentation arising from the results of the study must be reviewed and approved in writing by Jounce, in advance of submission. The review is aimed at protecting Jounce's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results or other information, generated or created in relation to the study must be carried out in accordance with the Clinical Study Agreement.

11.9.3. Confidentiality

Data collected during this study may be used to support the development, registration, or marketing of JTX-2011. After subjects have consented to take part in the study their medical records and the data collected during the study will be reviewed by Jounce and/or its representatives. These records and data may, in addition, be reviewed by the following: independent auditors who validate the data on behalf of Jounce; third parties with whom Jounce may develop, register or market JTX-2011; national or local regulatory authorities and the IRB(s) which gave its/their approval for this study to proceed.

Although subjects will be known by a unique number, their date of birth will also be collected and used to assist Jounce to verify the accuracy of the data, for example, that the laboratory results are assigned to the correct patient.

11.9.4. Audit / Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the U.S. FDA (as well as other national and local regulatory authorities), Jounce or its representatives, interested commercial parties and the IRB for each study site.

12. APPENDICES

12.1. Appendix 1: Schedules of Events

Table 11: Schedule of Assessments for Part A and B Dose Escalation (*closed to enrollment*)

(See Table 12 for Safety/PK/PD Expansion Cohorts AP1, AP2, BP1, BP2)

	Screening	Cycle 1					Cycle 2 and Beyond	End of Treatment	Long Term Follow-Up
Timing of Visit	Within 28 days of C1D1	Day 1[1]	Day 2	Day 4[2]	Day 8 ± 3	Day 15 ± 3	Day 1[1] ± 3	28 ± 7 days after last dose	Every 12 weeks following End of Treatment (±2 weeks)
Informed Consent	X								
Eligibility Criteria	X	X							
Medical History	X								
Demographics	X								
Physical Exam[3]	X	X	X	X	X	X	X	X	
Weight (kg)	X	X					X		
ECOG PS	X	X					X	X	
Electrocardiogram (ECG)[20]	X	X					X	X	
Vital Signs[4]	X	X	X	X	X	X	X	X	
Pregnancy test[5]	X	X					X	X	
Hematology	X	X[6]			X	X	X	X	
Chemistry	X	X[6]			X	X	X	X	
Coagulation Parameters	X	X[6]			X	X	X	X	
Thyroid Function	X	X[6]					X	X	
Urinalysis	X	X[6]					X	X	
Cytokines[7]		X	X				X	X	
JTX-2011 administration[24]		X					X		
Nivolumab administration[8,25] (Part B Only)		X					X		
Blood sample for Immunophenotyping[9]		X	X		X		X	X	

	Screening	Cycle 1					Cycle 2 and Beyond	End of Treatment	Long Term Follow-Up
Timing of Visit	Within 28 days of C1D1	Day 1[1]	Day 2	Day 4[2]	Day 8 ± 3	Day 15 ± 3	Day 1[3] ± 3	28 ± 7 days after last dose	Every 12 weeks following End of Treatment (±2 weeks)
Blood sample for Target Engagement[10]		X	X		X	X	X	X	
Pharmacokinetic sampling[11]		X	X		X	X	X	X	
ADA sampling[12]		X					X	X	
Blood Sample for JTXP[13]		X	X						
Neutralizing Antibody[14]		X					X	X	
RNA Blood Sample[15]		X					X		
DNA Blood Sample[15]		X							
Archival Tumor Tissue[16]	X								
CT scan[17]	X						X[17]	X[19]	X[23]
Response Assessment[18]		X					X	X[19]	
Concomitant Medications	X	X	X	X	X	X	X	X	
Adverse Events (AEs)	X	X	X	X	X	X	X	X	
Optional Brain MRI[21]	X								
Follow-up of ongoing AEs								X[22]	
Survival Status[24]									X
Confirmation of Progression									X

Parts A and B Footnotes:

[1]All assessments should be performed prior to JTX-2011 dosing unless otherwise noted.
[2]Visit required for sentinel subjects only.
[3]Complete PE required at Screening and End of Treatment visits; otherwise a targeted PE is acceptable per institutional guidelines. Height to be calculated at screening visit only.
[4]Vital signs to include temperature, heart rate, respiratory rate, blood pressure, and oxygen saturation. Vital signs should be taken prior to and at the end of JTX-2011 infusion.
[5]Negative serum or urine pregnancy test during the Screening Period for women of childbearing potential and negative urine pregnancy test prior to administration of JTX-2011 on Day 1 of each treatment cycle.
[6]Cycle 1 Day 1 labs do not need to be repeated if collected within 72 hours prior for Screening.
[7]Cytokines on C1D1 pre-dose, 1, 6, and 24-hours, pre-dose on D1 of all subsequent cycles (e.g. CXD1), AND in the event of an infusion reaction.
[8]Nivolumab dosing is for Part B only.
[9]Immunophenotyping C1D1 pre-dose, 6 and 24-hrs, any time on C1D8, and pre-dose on D1 of all subsequent cycles (e.g. CXD1) and End of Treatment.

[10]Target Engagement by flow cytometry; samples will be collected pre-dose, 1 hr and 24 hrs for Cycle 1 Day 1; any time during Cycle 1 Day 8 and Cycle 1 Day 15; pre-dose D1 of all subsequent cycles (e.g. CxD1) and End of Treatment.
[11]Refer to Table 18 for PK sampling time points. This applies to PK for both JTX-2011 and nivolumab.
[12]ADA sample will be collected pre-dose on D1 of all cycles (e.g. CXD1) and End of Treatment. This applies to both JTX-2011 and nivolumab (Part B).
[13]Blood samples for JTXP will be collected pre-dose and 24 hrs on Cycle 1 Day 1.
[14]NAb sample will be collected pre-dose before every cycle and at end of Treatment. This applies for both JTX-2011 and nivolumab (Part B).
[15]RNA sample will be collected on C1D1, C2D1 and C7D1. DNA Sample to be collected on C1D1 only.
[16]Please refer to Study Lab Manual for more details.
[17]CT scan or other imaging as needed to assess response every 3 cycles (within 28 days prior to Cycle 1 Day 1, then within 10 days prior to Day 1 of every 3rd cycle, e.g. C4, C7, C10, etc.). The imaging interval may be increased to every 12 weeks with a +/- 3 week window for subjects who remain on study treatment for ≥ 24 months.
[18]Identification and measurement of target lesions will be performed at Cycle 1 Day 1. Response will be determined by RECIST (Version 1.1) every 3 cycles until disease progression. The same method of assessment used at Cycle 1 Day 1 should be used throughout the study.
[19]Only required for subjects whose last assessment was > 9 weeks.
[20] 12-lead ECG to be read by site.
[21]Optional Brain MRI to determine eligibility of subjects with documented history of brain metastasis.
[22]Phone call assessment.
[23] CT scans will be conducted approximately every 12 weeks during the long-term follow-up period for subjects without confirmed progression during the treatment period. Once a patient has progressed via CT scan, one follow-up confirmatory CT scan will be obtained approximately 12 weeks later.
[24] Subjects will be observed for at least one hour after completion of JTX-2011 infusion for assessment of IV infusion tolerability.

Table 12: Schedule of Events in AP1 and AP2 and BP1 and BP2[17]

	Screening	Cycle 1				Cycle 2 and Beyond	End of Treatment	Long-Term Follow-up for
Timing of Visit	Within 28 days of C1D1	Day 1[1]	Day 2	Day 8 ± 3	Day 15 ± 3	Day 1 ± 3[1]	28 ± 7 days after last dose	Every 12 weeks following End of Treatment (±2 weeks)
Informed Consent	X							
Eligibility Criteria	X	X						
Medical History	X							
Demographics	X							
Physical Exam[2]	X	X	X	X	X	X	X	
Weight (kg)	X	X				X		
ECOG PS	X	X				X	X	
Electrocardiogram (ECG)[20]	X	X				X	X	
Vital Signs[3]	X	X	X	X	X	X	X	
Pregnancy test[4]	X	X				X	X	
Hematology	X	X[5]		X	X	X	X	
Chemistry	X	X[5]		X	X	X	X	
Coagulation Parameters	X	X[5]		X	X	X	X	
Thyroid Function	X	X[5]				X	X	
Urinalysis	X	X[5]				X	X	
Cytokines[6]		X	X			X	X	
JTX-2011 administration[24]		X				X		
Nivolumab administration[7,25] (Part BP 1 and BP Only)		X				X		
Blood sample for Immunophenotyping[8]		X	X	X		X	X	
Blood sample for Target Engagement[9]		X	X	X	X	X	X	
Pharmacokinetic sampling[10]		X	X	X	X	X	X	
ADA sampling[11]		X				X	X	
Blood Sample for JTXP[12]		X	X					
Neutralizing Antibody[13]		X				X	X	
RNA Blood Sample[14]		X				X		
DNA Blood Sample[14]		X						
Archival Tumor Tissue[15]	X							
Fresh Tumor Biopsy[16]	X					X[16]		
CT scan[17]	X					X[17]	X[19]	X[23]

	Screening	Cycle 1				Cycle 2 and Beyond	End of Treatment	Long-Term Follow-up for
Timing of Visit	Within 28 days of C1D1	Day 1[1]	Day 2	Day 8 ± 3	Day 15 ± 3	Day 1 ± 3[1]	28 ± 7 days after last dose	Every 12 weeks following End of Treatment (±2 weeks)
Response Assessment[18]		X				X	X[19]	
Concomitant Medications	X	X	X	X	X	X	X	
Adverse Events (AEs)	X	X	X	X	X	X	X	
Optional Brain MRI[21]	X							
Follow-up of ongoing AEs								X[22]
Survival Status[24]								X
Confirmation of Progression								X

[1]All assessments should be performed prior to JTX-2011 dosing unless otherwise noted.
[2]Complete PE required at Screening and End of Treatment visits; otherwise a targeted PE is acceptable per institutional guidelines. Height to be calculated at screening visit only.
[3]Vital signs to include temperature, heart rate, respiratory rate, blood pressure, and oxygen saturation. Vital signs should be taken prior to and at the end of infusion.
[4]Negative serum or urine pregnancy test during the Screening Period for women of childbearing potential and negative urine pregnancy test prior to administration of JTX-2011 on Day 1 of each treatment cycle.
[5]Cycle 1 Day 1 labs do not need to be repeated if collected within 72 hours prior for Screening.
[6]Cytokines on C1D1 pre-dose, 1, 6, and 24-hours, pre-dose on D1 of all subsequent cycles (e.g. CXD1), AND in the event of an infusion reaction.
[7]Nivolumab dosing is for Part BP1 and BP2 only.
[8]Immunophenotyping C1D1 pre-dose, 6 and 24-hrs, any time on C1D8, and pre-dose on D1 of all subsequent cycles (e.g. CXD1) and End of Treatment.
[9]Target Engagement by flow cytometry; samples will be collected pre-dose, 1 hr and 24 hrs for Cycle 1 Day 1; any time during Cycle 1 Day 8 and Cycle 1 Day 15; pre-dose D1 of all subsequent cycles (e.g. CxD1) and End of Treatment.
[10]Refer to Table 19 for PK sampling time points. This applies to PK for both JTX-2011 (all cohorts) and nivolumab (Part BP1 and BP2).
[11]ADA sample will be collected pre-dose on D1 of all cycles (e.g. CXD1) and End of Treatment. This applies to both JTX-2011 and nivolumab (Part BP1 and BP2).
[12]Blood samples for JTXP will be collected pre-dose and 24 hrs on Cycle 1 Day 1.
[13]NAb sample will be collected pre-dose before every cycle and at end of Treatment. This applies for both JTX-2011 and nivolumab (Part BP1 and BP2).
[14]RNA sample will be collected on C1D1, C2D1 and C7D1. DNA Sample to be collected on C1D1 only.
[15]Please refer to Study Lab Manual for more details.
[16]Fresh Tumor biopsies will be obtained pre-treatment and between C2D1 and C3D1. Please refer to Study Lab Manual for processing and shipping instructions. Collection procedure should follow local practice guidelines.
[17]CT scan or other imaging as needed to assess response every 3 cycles (within 28 days prior to Cycle 1 Day 1, then within 10 days prior to Day 1 of every 3rd cycle, e.g. C4, C7, C10, etc.). The imaging interval may be increased to every 12 weeks with a +/- 3 week window for subjects who remain on study treatment for ≥ 24 months.
[18]Identifiifcation and measurement of target lesions will be performed at Cycle 1 Day 1. Response will be determined by RECIST (Version 1.1) every 3 cycles until disease progression. The same method of assessment used at Cycle 1 Day 1 should be used throughout the study.
[19]Only required for subjects whose last assessment was > 9 weeks.
[20]12-lead ECG to be read by site.

[21]Optional Brain MRI to determine eligibility of subjects with documented history of brain metastasis.
[22]Phone call assessment.
[23] CT scans will be conducted approximately every 12 weeks during the long-term follow-up period for subjects without confirmed progression during the treatment period. Once a patient has progressed via CT scan, one follow-up confirmatory CT scan will be obtained approximately 12 weeks later.
[24] Subjects will be observed for at least one hour after completion of JTX-2011 infusion for assessment of IV infusion tolerability.
[25] Subjects will be observed for at least one hour after completion of JTX-2011 and nivolumab infusions for assessment of IV infusion tolerability.

Table 13: Phase 1 q6w in Part E (JTX-2011 + Ipilimumab)

	Screening	Cycle 1						Cycle 2		Cycle 3		Cycle 4		Cycle 5 and Beyond		End of Treatment	Long-Term Follow-up
Timing of Visit	Within 28 days of C1D1	Day 1	Day 2	Day 4[2]	Day 8	Day 15	Day 22	Day 1 +3	Day 22 ±3	Day 1 ±3	Day 22 ±3	Day 1 ±3	Day 22 ±3	Day 1 ±3	Day 22 ±3	28 ± 7 days after last dose	Every 12 weeks following End of Treatment (± 2 weeks)
Informed Consent	X																
Eligibility Criteria	X	X															
Medical History	X																
Demographics	X																
Physical Exam[1]	X	X		X	X		X[5]	X[5]	X[5]	X[5]		X[5]		X[5]		X	
Weight (kg)	X	X					X[5]	X[5]	X[5]	X[5]		X[5]		X[5]			
ECOG PS	X	X						X[5]		X[5]		X[5]		X[5]		X	
ECG	X	X[5]						X[5]		X[5]		X[5]		X[5]		X	
Vital Signs[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy test[4]	X	X[5]						X[5]		X[5]		X[5]		X[5]			
Hematology[4]	X	X[5]			X	X	X	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X	
Chemistry[4]	X	X[5]			X	X	X	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X	
Coagulation Parameters[4]	X	X[5]			X	X	X	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X	
Thyroid Function[4]	X	X[5]						X[5]		X[5]		X[5]		X[5]		X	
Urinalysis[4]	X	X[5]						X[5]		X[5]		X[5]		X[5]		X	
PSA[16]		X[5]						X[5]		X[5]		X[5]		X[5]		X	
Cytokines[6]		X	X					X		X		X		X			
JTX-2011[7]		X						X		X		X		X			
Ipilimumab[8]		X					X[17]	X[17]	X[17]								
IP[6]	X	X	X		X		X	X	X	X	X	X	X	X	X		
TE[6]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
PK[6]		X	X		X	X	X	X	X	X[18]	X[18]	X[18]	X[18]	X[18]	X[18]	X	
ADA[6]		X					X	X	X	X[18]	X[18]	X[18]	X[18]	X[18]	X[18]	X	
Archival Tumor[6]	X																
NAb[6]		X					X	X	X	X[18]	X[18]	X[18]	X[18]	X[18]	X[18]	X	
DNA[6]		X															
RNA[6]		X						X				X					
Radiologic Assessment[9]	X	Performed every 9 or 12 weeks (-10 days) from C1D1[10]														X[11]	X[12]
Bone Scan[16]	X	Performed every 12 (-10 days) weeks from C1D1														X	
ConMeds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[13]
Optional Brain MRI[14]	X																
Survival Status																	X[15]

Part E Footnotes:
[1] A Complete physical exam is required at Screening and End of Treatment; otherwise a targeted physical exam is acceptable per institutional guidelines. Height to be calculated at screening visit only.
[2] Day 4 visit required for sentinel subjects only.
[3] Vital signs to include temperature, heart rate, respiratory rate, blood pressure, and oxygen saturation. Vital signs should be taken prior to and at the end of JTX-2011 infusion. For days in which ipilimumab is dosed alone (C1D22 and C2D22), vital signs should be taken pre- and post-dose of ipilimumab.
[4] Refer to Section 8.8 for specific lab parameters. Pregnancy test can be serum or urine.
[5] Do not need to be repeated if collected within 72 hours prior to visit.
[6] Refer to the Study Lab Manual for processing/shipping instructions. For specific blood sampling time points, refer to Table 21

[7] Subjects should be observed for at least 1-hour post-JTX-2011 infusion.
[8] Subjects should be observed for at least 1-hour post-ipilimumab infusion.
[9] Response will be determined by RECIST (Version 1.1). Prostate cancer lesions to be assessed per the PCWG2 guidelines {Scher 2008}. The same method of assessment used at baseline should be used throughout the study.
[10] With the exception of prostate cancer patients, radiologic assessments will be performed every 9 weeks (-10 days), or approximately every 1.5 cycles (e.g., mid-Cycle 2, end of Cycle 3, mid-Cycle 5, end of Cycle 6, etc.) until disease progression. The imaging interval may be increased to every 12 weeks with a +/- 3 week window for subjects who remain on study treatment for ≥ 24 months.
Prostate cancer subjects to have radiographic imaging every 12 weeks (-10 days), or approximately at the end of every 2 cycles. The same method of assessment used at baseline should be used throughout the study.
[11] Only required for subjects whose last assessment was > 9 weeks (or > 12 weeks for prostate cancer subjects).
[12] For subjects discontinuing treatment for reasons other than disease progression, radiologic assessment will be conducted every 12 weeks (± 2 weeks) during the long-term follow-up period until confirmed disease progression or another anti-cancer therapy is initiated.
[13] Adverse events will be followed up to 28 days post last dose. As the EOT visit can occur anywhere between 21-35 days post last dose any ongoing AEs at the time of the EOT visit can be followed via other contact (e.g., phone or email) up to 28 days post dose. If an SAE occurs 28 days after last dose administered, the event will only be followed if assessed to be at least possibly related to study drug.
[14] Optional Brain MRI to determine eligibility of subjects with documented history of brain metastasis.
[15] Survival can be followed via phone call or email, a clinic visit is not required.
[16] For subjects with prostate cancer only.
[17] If ipilimumab doses are missed on C1D22, C2D1, or C2D22, they can be made up q3w beginning on C3D1. Each subject may receive up to four total doses of ipilimumab.
[18] Ipilimumab PK, ADA, and NAb are only to be collected on C3D1 and beyond if ipilimumab is administered at those visits.

Table 14: Phase 1 q3w in Part G (JTX-2011 + Pembrolizumab)

	Screening	Cycle 1					Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8 and Beyond	End of Treatment	Long-Term Follow-up
Timing of Visit	Within 28 days of C1D1	Day 1	Day 2	Day 4[14]	Day 8	Day 15	Day 1 +3	Day 1 ±3	Day 1 ±3	Day 1 ±3	Day 1 ±3	Day 1 ±3	Day 1 ±3	28 ± 7 days post last dose	Every 12 weeks post last dose (± 2 weeks)
Informed Consent	X														
Eligibility Criteria	X	X													
Medical History	X														
Demography	X														
Physical Exam[1]	X	X		X	X		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X	
Weight (kg)	X	X					X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]		
ECOG PS	X	X					X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X	
ECG	X	X[4]					X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X	
Vital Signs[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy test[3]	X	X[4]					X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]		
Hematology[3]	X	X[4]			X	X	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X	
Chemistry[3]	X	X[4]			X	X	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X	
Coagulation Parameters[3]	X	X[4]			X	X	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X	
Thyroid Function[3]	X	X[4]					X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X	
Urinalysis[3]	X	X[4]					X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X	
Cytokines[5]		X	X				X	X	X	X	X	X	X		
JTX-2011[6]		X					X	X	X	X	X	X	X		
Pembrolizumab[7]		X					X	X	X	X	X	X	X		
IP[5]	X	X	X		X		X	X	X	X	X	X	X		
TE[5]	X	X	X		X	X	X	X	X	X	X	X	X	X	
PK[5]		X	X		X	X	X	X	X	X	X	X	X	X	
ADA[5]		X					X	X	X	X	X	X	X	X	
Archival Tumor Tissue[5]	X														
Fresh Biopsy[5]	X														
NAb[5]		X					X	X	X	X	X	X	X	X	
DNA Blood Sample[5]		X													
RNA Blood Sample[5]		X					X					X			
Radiologic Assessment[8]	X								X			X		X[9]	X[10]
ConMeds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X[11]	
Optional Brain MRI[12]	X														
Survival Status															X[13]

Part G Footnotes:
[1] A complete physical exam is required at Screening and End of Treatment; otherwise a targeted physical exam is acceptable per institutional guidelines. Height to be calculated at screening visit only.
[2] Vital signs to include temperature, heart rate, respiratory rate, blood pressure, and oxygen saturation. Vital signs should be taken prior to and at the end of JTX-2011 infusion.
[3] Refer to Section 8.8 for specific lab parameters. Pregnancy test can be serum or urine.
[4] Do not need to be repeated if collected within 72 hours prior to visit.
[5] Refer to the Study Lab Manual for processing/shipping instructions. For specific blood sampling time points, refer to Table 23.
[6] Subjects should be observed for at least 1 hour post-JTX-2011 infusion.
[7] Subjects should be observed for at least 1 hour post-pembrolizumab infusion.
[8] Response will be determined by RECIST (Version 1.1) every 9 weeks (-10 days) prior to Day 1 of every 3rd cycle, (e.g. C4, C7, C10, etc.) until disease progression. The imaging interval may be increased to every 12 weeks with a +/- 3 week window for subjects who remain on study treatment for ≥ 24 months.
The same method of assessment used at baseline should be used throughout the study.
[9] Only required for subjects whose last assessment was > 9 weeks.
[10] For subjects discontinuing treatment for reasons other than disease progression, radiologic assessment will be conducted every 12 weeks (± 2 weeks) during the long-term follow-up period until confirmed disease progression or another anti-cancer therapy is initiated.
[11] Adverse events will be followed up to 28 days post last dose. As the EOT visit can occur anywhere between 21-35 days post last dose, any outstanding AEs at the time of the EOT visit can be followed via other contact (e.g., phone or email) up to 28 days post dose. If an SAE occurs after 28 days after last dose administered, the event will only be followed if assessed to be at least possibly related to study drug.
[12] Optional Brain MRI to determine eligibility of subjects with documented history of brain metastasis.
[13] Survival can be followed via phone call or email, a clinic visit is not required.
[14] Day 4 visit required for sentinel subjects only.

Table 15: Phase 2 q3w in Parts C (JTX-2011), D (JTX-2011 + Nivolumab), and H (JTX-2011 + Pembrolizumab)[16]

	Screening	Cycle 1		Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8 and Beyond	End of Treatment	Long-Term Follow-up
Timing of Visit	Within 28 days of C1D1	Day 1	Day 2	Day 1 ± 3	Day 1 ± 3	Day 1 ± 3	Day 1 ±3	Day 1 ±3	Day 1 ± 3	Day 1 ± 3	28 ± 7 days post-last dose	Every 12 weeks post-last dose (± 2 weeks)
Informed Consent	X											
Eligibility Criteria	X	X										
Medical History	X											
Demography	X											
Physical Exam[1]	X	X		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X	
Weight (kg)	X	X		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]		
ECOG PS	X	X		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X	
ECG	X	X[4]		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X	
Vital Signs[2]	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy Test[3]	X	X[4]		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]		
Hematology[3]	X	X[4]		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X	
Chemistry[3]	X	X[4]		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X	
Coagulation Parameters[3]	X	X[4]		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X	
Thyroid Function[3]	X	X[4]		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X	
Urinalysis[3]	X	X[4]		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X	
Cytokines[5]		X	X	X	X	X	X	X	X	X		
JTX-2011[6]		X		X	X	X	X	X	X	X		
Nivolumab[7] (Part D only)		X		X	X	X	X	X	X	X		
Pembrolizumab[8] (Part H only)		X		X	X	X	X	X	X	X		
Post-Progression Nivolumab or Pembrolizumab (Part C only)		See Table 17										
IP[5]	X	X	X	X	X	X	X	X	X	X		
TE[5]	X	X	X	X	X	X	X	X	X	X	X	
PK[5]		X	X	X	X	X	X	X	X	X	X	
ADA[5]		X		X	X	X	X	X	X	X	X	
NAb[5]		X		X	X	X	X	X	X	X	X	
DNA Blood Sample[5]		X										
RNA Blood Sample[5]		X		X					X			
Archival Tumor[5]	X											
Fresh Tumor Biopsy[5]	X			X[9]								
Radiologic Assessment[10]	X					X			X		X[11]	X[12]
ConMeds	X	X	X	X	X	X	X	X	X	X	X	
AEs	X	X	X	X	X	X	X	X	X	X	X[13]	
Optional Brain MRI[14]	X											
Survival Status												X[15]

Parts C, D, and H Footnotes (q3w):

[1] A complete physical exam is required at Screening and End of Treatment; otherwise a targeted physical exam is acceptable per institutional guidelines. Height to be calculated at screening visit only.

[2] Vital signs to include temperature, heart rate, respiratory rate, blood pressure, and oxygen saturation. Vital signs should be taken prior to and at the end of JTX-2011 infusion.

[3] Refer to Section 8.8 for specific lab parameters. Pregnancy test can be serum or urine.

[4] Do not need to be repeated if collected within 72 hours prior to visit.

[5] Refer to the Study Lab Manual for processing shipping instructions. For specific blood sampling time points, refer to Table 18 (Part C), Table 20 (Part D), or Table 20 (Part H).

[6] Subjects should be observed for at least 1 hour post-infusion.

[7] Subjects should be observed for at least 1 hour post-nivolumab infusion.

[8] Subjects should be observed for at least 1 hour post-pembrolizumab infusion.

[9] Part C only. On-treatment biopsies can be collected any time after dosing on C2D1 and prior to dosing on C3D1.

[10] Response will be determined by RECIST (Version 1.1) or modified RECIST (for mesothelioma subjects in Part C only) every 9 weeks (-10 days) prior to Day 1 of every 3rd cycle (e.g. C4, C7, C10, etc.).The imaging interval may be increased to every 12 weeks with a +/- 3 week window for subjects who remain on study treatment for ≥ 24 months. The same method of assessment used at baseline should be used throughout the study.

[11] Only required for subjects whose last assessment was > 9 weeks.

[12] For subjects discontinuing treatment for reasons other than disease progression, radiologic assessment will be conducted every 12 weeks (± 2 weeks) during the long-term follow-up period until confirmed disease progression or another anti-cancer therapy is initiated.

[13] Adverse events will be followed up to 28 days post last dose. As the EOT visit can occur anywhere between 14-28 days post last dose, any outstanding AEs at the time of the EOT visit can be followed via other contact (e.g., phone or email) up to 28 days post dose. If an SAE occurs more than 28 days after last dose administered, the event will only be followed if assessed to be at least possibly related to study drug.

[14] Optional Brain MRI to determine eligibility of subjects with documented history of brain metastasis.

[15] Survival can be followed via phone call or email, a clinic visit is not required.

[16] JTXP previously collected for protocol version 5.0.

Table 16: Phase 2 q6w in Parts C (JTX-2011), F (JTX-2011 + Ipilimumab), and H (JTX-2011 + Pembrolizumab)

	Screening	Cycle 1			Cycle 2		Cycle 3		Cycle 4		Cycle 5 and Beyond		End of Treatment	Long-Term Follow-up
Timing of Visit	Within 28 days of C1D1	Day 1	Day 2	Day 22 ±3	Day 1 ± 3	Day 22 ± 3	Day 1 ± 3	Day 22 ± 3	Day 1 ± 3	Day 22 ±3	Day 1 ± 3	Day 22 ± 3	28 ± 7 days post last dose	Every 12 weeks post-last dose (± 2 weeks)
Informed Consent	X													
Eligibility Criteria	X	X												
Med Hx and Demography	X													
Physical Exam[1]	X	X		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X	
Weight (kg)	X	X		X[4,18]	X[4]	X[4,18]	X[4]	X[4,19]	X[4]	X[4,19]	X[4]	X[4,19]		
ECOG PS	X	X			X[4]		X[4]		X[4]		X[4]		X	
ECG	X	X[4]			X[4]		X[4]		X[4]		X[4]		X	
Vital Signs[2]	X	X	X	X[4]	X	X[4]	X	X[4]	X	X[4]	X	X[4]	X	
Pregnancy test[3]	X	X[4]			X[4]		X[4]		X[4]		X[4]			
Hematology	X	X[4]		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X	
Chemistry[3]	X	X[4]		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X	
Coagulation Parameters[3]	X	X[4]		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X	
Thyroid Function[3]	X	X[4]			X[4]		X[4]		X[4]		X[4]		X	
Urinalysis[3]	X	X[4]			X[4]		X[4]		X[4]		X[4]		X	
PSA[17]		X			X		X		X		X		X	
Cytokines[5]		X	X		X		X		X		X			
JTX-2011[6]		X			X		X		X		X			
Ipilimumab (Part F only)[7]		X		X[20]	X[20]	X[20]								
Pembrolizumab (Part H only)[8]		X		X	X	X	X	X	X	X	X	X		
Post-Progression Nivolumab or Pembrolizumab (Part C only)		See Table 17												
IP[5]	X	X	X	X	X	X	X	X	X	X	X	X		
TE[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK[5]		X	X	X	X	X	X[21]	X[21]	X[21]	X[21]	X[21]	X[21]	X	
ADA[5]		X		X	X	X	X[21]	X[21]	X[21]	X[21]	X[21]	X[21]	X	
NAb[5]		X		X	X	X	X[21]	X[21]	X[21]	X[21]	X[21]	X[21]	X	
DNA Blood Sample[5]		X												
RNA Blood Sample[5]		X			X				X					
Archival Tumor[5]	X													
Fresh Tumor Biopsy[5]	X				X[9]									
Radiologic Assessment[10]	X	Performed every 9 or 12 weeks (-10 days) from C1D1[11]											X[12]	X[13]
Bone Scan[17]	X	Performed every 12 weeks (-10 days) from C1D1											X	
ConMeds	X	X	X	X	X	X	X	X	X	X	X	X	X	
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X[14]	
Optional Brain MRI[15]	X													
Survival Status														X[16]

Parts C, F, and H Footnotes (q6w):

[1] A complete physical exam is required at Screening and End of Treatment; otherwise a targeted physical exam is acceptable per institutional guidelines. Height to be calculated at screening visit only.

[2] Vital signs to include temperature, heart rate, respiratory rate, blood pressure, and oxygen saturation. Vital signs should be taken prior to and at the end of JTX-2011 infusion. For days in which pembrolizumab or ipilimumab are dosed alone (i.e., D22 of each cycle), vital signs should be taken pre-and post-dose.

[3] Refer to Section 8.8 for specific lab parameters. Pregnancy test can be serum or urine.

[4] Labs do not need to be repeated if collected within 72 hours prior to visit.

[5] Refer to the Study Lab Manual for processing/shipping instructions. For specific blood sampling time points, refer to Table 18 (Part C), Table 22 (Part F), or Table 22 (Part H).

[6] Subjects should be observed for at least 1 hour post-JTX-2011 infusion.

[7] Subjects should be observed for at least 1 hour post-ipilimumab infusion.

[8] Subjects should be observed for at least 1 hour post-pembrolizumab infusion.

[9] Parts C and F only. On-treatment biopsies can be collected any time after dosing on C2D1 and prior to the C2D22 visit.

[10] Response will be determined by RECIST (Version 1.1). Prostate cancer lesions to be assessed per the PCWG2 guidelines (Scher 2008). The same method of assessment used at baseline should be used throughout the study.

[11] Response will be determined by RECIST (Version 1.1) every 9 weeks (-10 days), or approximately every 1.5 cycles (e.g., mid-Cycle 2, end of Cycle 3, mid-Cycle 5, end of Cycle 6, etc.). The imaging interval may be increased to every 12 weeks with a +/- 3 week window for subjects who remain on study treatment for ≥ 24 months.
cancer subjects to have radiographic imaging every 12 weeks (-10 days) or approximately at the end of every 2 cycles.

[12] Only required for subjects whose last assessment was > 9 weeks (or > 12 weeks for prostate cancer subjects).

[13] For subjects discontinuing treatment for reasons other than disease progression, radiologic assessment will be conducted every 12 weeks (± 2 weeks) during the long-term follow-up period until confirmed disease progression or another anti-cancer therapy is initiated.

[14] Adverse events will be followed up to 28 days post last dose. As the EOT visit can occur anywhere between 14-28 days post last dose, any outstanding AEs at the time of the EOT visit can be followed via other contact (e.g., phone or email) up to 28 days post dose. If an SAE occurs after 28 days after last dose administered, the event will only be followed if assessed to be at least possibly related to study drug.

[15] Optional Brain MRI to determine eligibility of subjects with documented history of brain metastasis.

[16] Survival can be followed via phone call or email, a clinic visit is not required.

[17] For subjects with prostate cancer only.

[18] Weight required for Parts F and H subjects only.

[19] Weight required for Part H subjects only.

[20] If ipilimumab doses are missed on C1D22, C2D1, or C2D22, they can be made up q3w beginning on C3D1. Each subject may receive up to four total doses of ipilimumab.

[21] Ipilimumab PK, ADA, and NAb are only to be collected on C3D1 and beyond if ipilimumab is administered at those visits.

Table 17: Post-Progression in Part C (JTX-2011 + Nivolumab or Pembrolizumab)

	Cycle X		End of Treatment	Long-Term Follow-up
Timing of Visit	Day 1 ± 3 days	Day 22[3] ± 3 days	28 ± 7 days post last dose	Every 12 weeks post-last dose (± 2 weeks)
Informed Consent	X[1]			
Eligibility Criteria	X[2]			
Physical Exam[4]	X	X	X	
Weight (kg)	X[7]	X[7]		
ECOG PS	X[7]	X[7]	X	
ECG	X[7]		X	
Vital Signs[5]	X	X[7]	X	
Pregnancy test[6]	X[7]			
Hematology[6]	X[7]	X[7]	X	
Chemistry[6]	X[7]	X[7]	X	
Coagulation Parameters[6]	X[7]	X[7]	X	
Thyroid Function[6]	X[7]		X	
Urinalysis[6]	X[7]		X	
JTX-2011[8]	X			
Nivolumab or Pembrolizumab[9]	X	X		
Radiologic Assessment[10]			X[11]	
ConMeds	X	X	X	
AEs	X	X	X[12]	
Survival Status				X[13]

[1] The subject should be re-consented with the addition of nivolumab or pembrolizumab to their treatment regimen.
[2] Eligibility should be confirmed prior to first dose.
[3] Only for subjects enrolled to the q6w dosing schedule in Part C.
[4] A complete physical exam is required at End of Treatment; otherwise a targeted physical exam is acceptable per institutional guidelines.
[5] Vital signs to include temperature, heart rate, respiratory rate, blood pressure, and oxygen saturation. Vital signs should be taken prior to and at the end of JTX-2011 infusion. For days in which nivolumab or pembrolizumab is dosed alone (CXD22), vital signs should be taken pre-and post-dose.
[6] Refer to Section 8.8 for specific lab parameters. Pregnancy test can be serum or urine.
[7] Assessments do not need to be repeated if collected within 72 hours prior to visit.
[8] Subjects should be observed for at least 1 hour post-JTX-2011 infusion.
[9] Subjects should be observed for at least 1 hour post-nivolumab or pembrolizumab infusion.
[10] Radiologic assessment will be performed every 9 weeks (-10 days). The imaging interval may be increased to every 12 weeks with a +/- 3 week window for subjects who remain on study treatment for ≥ 24 months.
The same method of assessment used at baseline should be used throughout the study.
[11] Only required for subjects whose last assessment was > 9 weeks.

[12] Adverse events will be followed up to 28 days post last dose. As the EOT visit can occur anywhere between 21-35 days post last dose, any outstanding AEs at the time of the EOT visit can be followed via other contact (e.g., phone or email) up to 28 days post dose. If an SAE occurs after 28 days after last dose administered, the event will only be followed if assessed to be at least possibly related to study drug.
[13] Survival can be followed via phone call or email, a clinic visit is not required.

Table 18: Sample Collection Timepoints for Part A (Including AP1 and AP2) and C

			Part A Sample Type								Part C Sample Type							
Cycle #	**Visit Name**	**Time Point**	**PK[4]**	**ADA**	**NAb**	**Cytokines**	**TE**	**IP**	**RNA**	**DNA**	**PK**	**ADA**	**NAb**	**Cytokines**	**TE**	**IP**	**RNA**	**DNA**
n/a	Screening	*Anytime*													X	X[3]		
Cycle 1	Day 1	*0h*	X	X	X	X	X	X	X	X	X	X	X	X	X	X[3]	X	X
		30m	X															
		1h	X			X	X				X			X	X			
		1h 30m ± 10m	X															
		4h ± 10m	X															
		6h ± 10m	X			X								X				
	Day 2	*24h ± 4h*	X			X	X	X			X			X	X	X		
	Day 8	*Any time*	X				X	X										
	Day 15	*Any time*	X				X											
	Day 22[2]	*Any time*									X				X	X		
Cycle 2	Day 1	*0h*	X	X	X	X	X	X	X		X	X	X	X	X	X[3]	X	
		1h	X			X					X			X	X	X[3]		
	Day 22[2]	*Any time*									X				X	X		
Cycle 3	Day 1	*0h*	X	X	X	X	X	X			X	X	X	X	X	X[3]		
		1h	X			X					X			X	X	X[3]		
	Day 22[2]	*Any time*									X				X	X		
Cycle 4	Day 1	*0h*	X	X	X	X	X	X			X	X	X	X	X	X[3]	X[2]	
		1h	X			X					X			X	X	X[3]		
	Day 22[2]	*Any time*									X				X	X		
Cycle 5	Day 1	*0h*	X	X	X	X	X	X			X	X	X	X	X	X[3]		
		1h	X			X					X			X	X	X[3]		
	Day 22[2]	*Any time*									X				X	X		
Cycle 6	Day 1	*0h*	X	X	X	X	X	X			X	X	X	X	X	X[3]		
		1h	X			X					X			X	X	X[3]		
	Day 22[2]	*Any time*									X				X	X		
Cycle 7	Day 1	*0h*	X	X	X	X	X	X	X		X	X	X	X	X	X[3]	X[1]	
		1h	X			X					X			X	X	X[3]		
	Day 22[2]	*Any time*									X				X	X		
Cycle 8 and Beyond	Day 1	*0h*	X	X	X	X	X	X	X		X	X	X	X	X	X[3]		
		1h	X			X					X			X	X	X[3]		
	Day 22[2]	*Any time*									X				X	X		
	EOT	*28d ± 7d post-dose*	X	X	X		X				X	X	X		X	X[3]		

[1] q3w dosing only; [2] q6w dosing only; [3] Based on emerging data, certain subjects may be selected to have additional exploratory immunophenotyping involving additional blood draw(s). The site will be contacted directly by the Sponsor and informed which, if any patients, for whom this extra CPT tube(s) will be requested; [4]Time points refer to the time from the start of the JTX-2011 infusion. The 1 hour sample should be drawn just prior to the end of JTX-2011 infusion (approximately 5-10 minutes BEFORE the end of infusion)

Table 19: Sample Collection Schedule for Part B (Including BP1 and BP2)

			JTX-2011								Nivolumab		
Cycle #	**Visit Name**	**Time Point**	**PK[1]**	**ADA**	**NAb**	**Cytokines**	**TE**	**IP**	**RNA**	**DNA**	**PK**	**ADA**	**NAb**
Cycle 1	Day 1	*0h*	X	X	X	X	X	X	X	X	X	X	X
		30m	X										
		1h	X			X	X						
		1h 30m ± 10m	X								X		
		2h 30m ± 10m	X								X		
		4h ± 10m	X								X		
		6h ± 10m	X			X					X		
	Day 2	*24h ± 4h*	X			X	X	X			X		
	Day 8	*Any time*	X				X	X			X		
	Day 15	*Any time*	X				X				X		
Cycle 2	Day 1	*0h*	X	X	X	X	X	X	X		X	X	X
		1h	X			X							
Cycle 3	Day 1	*0h*	X	X	X	X	X	X			X	X	X
		1h	X			X							
Cycle 4	Day 1	*0h*	X	X	X	X	X	X			X	X	X
		1h	X			X							
Cycle 5	Day 1	*0h*	X	X	X	X	X	X			X	X	X
		1h	X			X							
Cycle 6	Day 1	*0h*	X	X	X	X	X	X			X	X	X
		1h	X			X							
Cycle 7	Day 1	*0h*	X	X	X	X	X	X	X		X	X	X
		1h	X			X							
Cycle 8 and Beyond	Day 1	*0h*	X	X	X	X	X	X			X	X	X
		1h	X			X							
	EOT	*28d ± 7d post-dose*	X	X	X		X				X	X	X

[1]Time points refer to the time from the start of the JTX-2011 infusion. The 1 hour sample should be drawn just prior to the end of JTX-2011 infusion (approximately 5-10 minutes BEFORE the end of the infusion)

Table 20: Sample Collections Schedule for Part D

			JTX-2011								Nivolumab		
Cycle #	**Visit Name**	**Time Point**	**PK[2]**	**ADA**	**NAb**	**Cytokines**	**TE**	**IP**	**RNA**	**DNA**	**PK**	**ADA**	**NAb**
n/a	Screening	*Anytime*					X	X[1]					
Cycle 1	Day 1	*0h*	X	X	X	X	X	X[1]	X	X	X	X	X
		1h	X			X	X						
		6h				X							
	Day 2	*24h ± 4h*	X			X	X	X			X		
Cycle 2	Day 1	*0h*	X	X	X	X	X	X[1]	X		X	X	X
		1h	X			X	X	X[1]					
Cycle 3	Day 1	*0h*	X	X	X	X	X	X[1]			X	X	X
		1h	X			X	X	X[1]					
Cycle 4	Day 1	*0h*	X	X	X	X	X	X[1]			X	X	X
		1h	X			X	X	X[1]					
Cycle 5	Day 1	*0h*	X	X	X	X	X	X[1]			X	X	X
		1h	X			X							
Cycle 6	Day 1	*0h*	X	X	X	X	X	X[1]			X	X	X
		1h	X			X							
Cycle 7	Day 1	*0h*	X	X	X	X	X	X[1]	X		X	X	X
		1h	X			X							
Cycle 8 and Beyond	Day 1	*0h*	X	X	X	X	X	X[1]			X	X	X
		1h	X			X							
	EOT	*28d ± 7d post-dose*	X	X	X		X	X[1]			X	X	X

[1] Based on emerging data, certain subjects may be selected to have additional exploratory immunophenotyping involving additional blood draw(s). The site will be contacted directly by the Sponsor and informed which, if any patients, for whom this extra CPT tube(s) will be requested;
[2] Time points refer to the time from the start of the JTX-2011 infusion. The 1 hour sample should be drawn just prior to the end of JTX-2011 infusion (approximately 5-10 minutes BEFORE the end of infusion)

Table 21: Sample Collection Schedule for Part E

			JTX-2011								Ipilimumab		
Cycle #	**Visit Name**	**Time Point**	**PK[3]**	**ADA**	**NAb**	**Cytokines**	**TE**	**IP[2]**	**RNA**	**DNA**	**PK**	**ADA**	**NAb**
n/a	Screening	*Anytime*					X	X[2]					
	Day 1	*0h*	X	X	X	X	X	X[2]	X	X	X	X	X
		30m	X										
		1h	X			X	X						
		1h 30m ± 10m	X								X		
		3h ± 10m	X								X		
		4h ± 10m	X								X		
		6h ± 10m	X			X					X		
	Day 2	*24h ± 4h*	X			X	X	X			X		
	Day 8	*Any time*	X				X	X			X		
	Day 15	*Any time*	X				X				X		
	Day 22	*0h*	X				X	X[2]			X	X	X
Cycle 2	Day 1	*0h*	X	X	X	X	X	X[2]	X		X	X	X
		1h	X			X	X	X[2]					
	Day 22	*0h*	X				X	X[2]			X	X	X
Cycle 3	Day 1	*0h*	X	X	X	X	X	X[2]					
		1h	X			X	X	X[2]					
	Day 22	*Any time*	X				X	X[2]					
Cycle 4	Day 1	*0h*	X	X	X	X	X	X[2]	X				
		1h	X			X	X	X[2]			X[1]	X[1]	X[1]
	Day 22	*Anytime*	X				X	X[2]					
Cycle 5 and Beyond	Day 1	*0h*	X	X	X	X	X	X[2]					
		1h	X			X							
	Day 22	*Any time*	X				X	X[2]					
	EOT	*28d ± 7d post-dose*	X	X	X		X	X[2]					

[1] Pre-dose (0h) Ipilimumab PK, ADA, and NAb are to be collected on C3D1 or after only if ipilimumab is administered.

[2] Based on emerging data, certain subjects may be selected to have additional exploratory immunophenotyping involving additional blood draw(s). The site will be contacted directly by the Sponsor and informed which, if any patients, for whom this extra CPT tube(s) will be requested

[3] Time points refer to the time from the start of the JTX-2011 infusion. The 1 hour sample should be drawn just prior to the end of JTX-2011 infusion (approximately 5-10 minutes BEFORE the end of infusion)

Table 22: Sample Collection Schedule for Part F

			JTX-2011								Ipilimumab		
Cycle #	**Visit Name**	**Time Point**	**PK[3]**	**ADA**	**NAb**	**Cytokines**	**TE**	**IP[2]**	**RNA**	**DNA**	**PK**	**ADA**	**NAb**
n/a	**Screening**	*Anytime*					X	X[2]					
Cycle 1	**Day 1**	*0h*	X	X	X	X	X	X[2]	X	X	X	X	X
		1h	X			X	X						
	Day 2	*24h ± 4h*	X			X	X	X			X		
	Day 22	*0h*	X				X	X[2]			X	X	X
Cycle 2	**Day 1**	*0h*	X	X	X	X	X	X[2]	X		X	X	X
		1h	X			X	X	X[2]					
	Day 22	*0h*	X				X	X[2]			X	X	X
Cycle 3	**Day 1**	*0h*	X	X	X	X	X	X[2]					
		1h	X			X	X	X[2]					
	Day 22	*Any time*	X				X	X[2]					
Cycle 4	**Day 1**	*0h*	X	X	X	X	X	X[2]	X				
		1h	X			X	X	X[2]					
	Day 22	*Any time*	X				X	X[2]			X[1]	X[1]	X[1]
Cycle 5 and Beyond	**Day 1**	*0h*	X	X	X	X	X	X[2]					
		1h	X			X							
	Day 22	*Any time*	X				X	X[2]					
	EOT	*28d ± 7d post-dose*	X	X	X		X	X[2]					

[1] Pre-dose (0h) Ipilimumab PK, ADA, and NAb are to be collected on C3D1 or after only if ipilimumab is administered.

[2] Based on emerging data, certain subjects may be selected to have additional exploratory immunophenotyping involving additional blood draw(s). The site will be contacted directly by the Sponsor and informed which, if any patients, for whom this extra CPT tube(s) will be requested

[3] Time points refer to the time from the start of the JTX-2011 infusion. The 1 hour sample should be drawn just prior to the end of JTX-2011 infusion (approximately 5-10 minutes BEFORE the end of infusion)

Table 23: Sample Collection Schedule for Part G

			JTX-2011								Pembrolizumab		
Cycle #	**Visit Name**	**Time Point**	**PK[2]**	**ADA**	**NAb**	**Cytokines**	**TE**	**IP[1]**	**RNA**	**DNA**	**PK**	**ADA**	**NAb**
n/a	Screening	*Any time*					X	X[1]					
Cycle 1	Day 1	*0h*	X	X	X	X	X	X[1]	X	X	X	X	X
		30m	X										
		1h	X			X	X						
		1h 30m ± 10m	X								X		
		2h ± 10m	X								X		
		4h ± 10m	X								X		
		6h ± 10m	X			X	X	X			X		
	Day 2	*24h ± 4h*	X			X	X	X			X		
	Day 8	*Any time*	X				X	X			X		
	Day 15	*Any time*	X				X				X		
Cycle 2	Day 1	*0h*	X	X	X	X	X	X[1]	X		X	X	X
		1h	X			X	X	X[1]					
Cycle 3	Day 1	*0h*	X	X	X	X	X	X[1]			X	X	X
		1h	X			X	X	X[1]					
Cycle 4	Day 1	*0h*	X	X	X	X	X	X[1]			X	X	X
		1h	X			X	X	X[1]					
Cycle 5	Day 1	*0h*	X	X	X	X	X	X[1]			X	X	X
		1h	X			X							
Cycle 6	Day 1	*0h*	X	X	X	X	X	X[1]			X	X	X
		1h	X			X							
Cycle 7	Day 1	*0h*	X	X	X	X	X	X[1]	X		X	X	X
		1h	X			X							
Cycle 8 and beyond	Day 1	*0h*	X	X	X	X	X	X[1]			X	X	X
		1h	X			X							
	EOT	*28d ± 7d post-dose*	X	X	X		X	X[1]			X	X	X

[1] Based on emerging data, certain subjects may be selected to have additional exploratory immunophenotyping involving additional blood draw(s). The site will be contacted directly by the Sponsor and informed which, if any patients, for whom this extra CPT tube(s) will be requested; [2] Time points refer to the time from the start of the JTX-2011 infusion. The 1 hour sample should be drawn just prior to the end of JTX-2011 infusion (approximately 5-10 minutes BEFORE the end of infusion)

Table 24: Sample Collections Schedule for Part H

			JTX-2011								Pembrolizumab		
Cycle #	**Visit Name**	**Time Point**	**PK[4]**	**ADA**	**NAb**	**Cytokines**	**TE**	**IP[3]**	**RNA**	**DNA**	**PK**	**ADA**	**NAb**
n/a	**Screening**	*Any time*					X	X[3]					
Cycle 1	**Day 1**	*0h*	X	X	X	X	X	X[3]	X	X	X	X	X
		1h	X			X	X						
	Day 2	*24h ± 4h*	X			X	X	X			X		
	Day 22[2]	*0h*	X				X	X[3]			X	X	X
Cycle 2	**Day 1**	*0h*	X	X	X	X	X	X[3]	X		X	X	X
		1h	X			X	X	X					
	Day 22[2]	*0h*	X				X	X[3]			X	X	X
Cycle 3	**Day 1**	*0h*	X	X	X	X	X	X[3]			X	X	X
		1h	X			X	X	X[3]					
	Day 22[2]	*0h*	X				X	X[3]			X	X	X
Cycle 4	**Day 1**	*0h*	X	X	X	X	X	X[3]	X[2]		X	X	X
		1h	X			X	X	X[3]					
	Day 22[2]	*0h*	X				X	X[3]			X	X	X
Cycle 5	**Day 1**	*0h*	X	X	X	X	X	X[3]			X	X	X
		1h	X			X							
	Day 22[2]	*0h*	X				X	X[3]			X	X	X
Cycle 6	**Day 1**	*0h*	X	X	X	X	X	X[3]			X	X	X
		1h	X			X							
	Day 22[2]	*0h*	X				X	X[3]			X	X	X
Cycle 7	**Day 1**	*0h*	X	X	X	X	X	X[3]	X[1]		X	X	X
		1h	X			X							
	Day 22[2]	*0h*	X				X	X[3]			X	X	X
Cycle 8 and beyond	**Day 1**	*0h*	X	X	X	X	X	X[3]			X	X	X
		1h	X			X							
	Day 22[2]	*0h*	X				X	X[3]			X	X	X
	EOT	*28d ± 7d post-dose*	X	X	X		X	X[3]			X	X	X

[1] q3w dosing only
[2] q6w dosing only
[3] Based on emerging data, certain subjects may be selected to have additional exploratory immunophenotyping involving additional blood draw(s). The site will be contacted directly by the Sponsor and informed which, if any patients, for whom this extra CPT tube(s) will be requested
[4] Time points refer to the time from the start of the JTX-2011 infusion. The 1 hour sample should be drawn just prior to the end of JTX-2011 infusion (approximately 5-10 minutes BEFORE the end of infusion)

12.2. Appendix 2: Web links

12.2.1. CTCAE

The link to the Common Criteria for Adverse Events (CTCAE Version 4.03) is:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

12.2.2. FDA Guidance for Investigators

The below links are to the Guidance Documents for Investigators Responsibilities and Safety Reporting Requirements for INDs:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf

http://www.fda.gov/downloads/Drugs/.../Guidances/UCM187772.pdf

12.3. Appendix 3: ECOG Performance Status

ECOG Performance Status Scale	
Grade	*Description*
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physical strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about > 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

12.4. Appendix 4: RECIST

See Laboratory Manual for more information

http://ctep.cancer.gov/protocolDevelopment/docs/recist_guideline.pdf

{Eisenhauer }

12.5. Appendix 5: Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group.

https://www.ncbi.nlm.nih.gov/pubmed/18309951

12.6. Appendix 6: Modified RECIST criteria for assessment of response in malignant pleural mesothelioma.

https://www.ncbi.nlm.nih.gov/pubmed/14760119

12.7. Appendix 7: Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria.

https://www.ncbi.nlm.nih.gov/pubmed/19934295

12.8. Appendix 8: Creatinine Clearance Guidelines

For males:

Creatinine clearance (mL/min) = (140 - age) × weight (kg) / 0.814 × plasma creatinine (μmol/L)

For females:

Creatinine clearance (mL/min) = 0.85 × (140 - age) × weight (kg) / 0.814 × plasma creatinine (μmol/L)

Note: Variations include estimating ideal body weight from subject height in obese subjects.

Reference: Cockcroft DW and Gault MH. Nephron 1976; 16: 31-41

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