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

Sponsor:

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Confidentiality Statement

[redacted]

SIGNATURE PAGE

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, which authorizes that the content is acceptable based on the current planned protocol.

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ABBREVIATIONS

ADA	Anti-Drug Antibody
AE	Adverse Event
AUC	Area Under the Curve
AUC_{inf}	Area Under the Curve from Time 0 Extrapolated to Infinity
AUC_{last}	Area Under the Curve from Time 0 to the time of the last quantifiable concentration
BLQ	Below the Limit of Quantitation
BOR	Best Overall Response
BSA	Body Surface Area
C1D1	Cycle 1 Day 1
CD4	Cluster of Differentiation 4
CD8	Cluster of Differentiation 8
CI	Confidence Interval
C_{max}	Maximum Serum Concentration
CPS	Combined Positive Score
CR	Complete Response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-Lymphocyte-Associated Protein 4
DCR	Disease Control Rate

DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
dMMR	Mismatch repair deficient
DOR	Duration of Response
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eSAP	Exploratory Statistical Analysis Plan
FDA	Food and Drug Administration
HNSCC	Head and Neck Squamous Cell
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
ICOS	Inducible CO-Stimulator of T cells
ITT	Intent-to-Treat
irAE	immune-related Adverse Event(s)
IRR	Infusion Related Reactions
irRC	immune-related Response Criteria
MedDRA	Medical Dictionary for Regulatory Activities
MSI-H	Microsatellite Instability
MTD	Maximum Tolerated Dose
NA	Not applicable

NAb	Neutralizing Antibody
NCA	Non-compartmental Analysis
NCI	National Cancer Institute
NE	Not Evaluable
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
PFS	Progression Free Survival
PK	Pharmacokinetics
PK/PD	Pharmacokinetic/Pharmacodynamic
PR	Partial Response
PT	Preferred Term
RP2D	Recommended Phase 2 Dose
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAF	Safety Analysis Set
SD	Stable Disease
SLD	Sum of the longest diameters
SOC	System Organ Class

SPD	Sum of the products of perpendicular diameters
SRB	Safety Review Board
T_{max}	Time to maximum serum concentration
$t_{1/2}$	Terminal Elimination Half-life
Teff	T effector cells
TFL	Tables, Figures, Listings
TPS	Tumor Proportion Score
Treg	T regulatory cells
ULN	Upper Limit of Normal
Vdss	Volume of distribution at steady state

TRADEMARK INFORMATION

SAS	SAS (Statistical Analysis Software) is a registered trademark of SAS Institute Inc.

REVISION HISTORY

Version	Date	Summary of Revisions
1.0	04-Mar-2020	Final Version 1.0

1. PURPOSE

This purpose of this statistical analysis plan (SAP) is to provide detailed descriptions of data presentation including data listings, summary tables and figures and the statistical methodologies that will be used to analyse the study data to facilitate and validate conclusions regarding the study objectives.

1.1 DOCUMENTS, STANDARDS AND ROLES

1.1.1 DOCUMENTS

Material in this document is based on the following study-specific reference documents:

- Protocol JTX-2011-101 version 9.0 (Amendment 8) dated 30May 2019

1.1.2 STANDARDS

Statistical analyses are planned and conducted in accordance with the principles outlined by the International Conference on Harmonization (ICH) E9 guidelines.

Rave/iMedidata is the electronic data collection tool. Raw data is converted to SDTM and ADaM datasets for use in data analyses and data listings.

1.1.3 ROLES

The SAP and all associated datasets will be created and/or reviewed internally by Jounce biostatistics and data management department. The SAP will be approved (signed) prior to database lock.

2. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the analysis methods for protocol JTX-2011-101(version 9.0 [Amendment 8] dated 30May 2019). Details of the exact analysis to be done are outlined, including analysis methods for study endpoints relevant to primary/secondary objectives of the protocol. Analysis of study endpoints relevant to exploratory objectives of the protocol and additional exploratory analysis are not in scope of this SAP and will be documented separately in an exploratory analysis plan. No previous versions of the SAP have been approved. Following sign-off and approval, any updates for this SAP will require additional signatures and approval.

2.1 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.

2.2 RATIONALE FOR CLINICAL DEVELOPMENT

The approvals of immunotherapeutic checkpoint inhibitors ipilumumab, 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), melanoma, renal cell carcinoma, head and neck squamous cell cancer (HNSCC) and Hodgkin's lymphoma. 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 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 (ipilumumab) 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 IFNg, and signal via PI3K with an increase in T-bet expression. Of greatest interest, however, was the finding that in melanoma patients treated with ipilumumab, a sustained increase in the frequency of ICOS-positive CD4 T cells correlated with clinical benefit and improved survival (see Figure 1 in protocol). This clinical translational data, which has been confirmed by others{Wang 2012}, suggested direct agonism of the ICOS pathway might be therapeutically beneficial for patients.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1 STUDY OBJECTIVES

3.1.1 PRIMARY OBJECTIVES FOR PARTS A AND B (PHASE 1)

- Assess the safety and tolerability of JTX-2011 (Part A) and JTX-2011 in combination with nivolumab therapy (Part B) in subjects with advanced solid tumor malignancies after single and multiple ascending doses of JTX-2011;
- 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) in subjects with advanced solid tumor malignancies.

3.1.2 SECONDARY OBJECTIVES FOR PARTS A AND B (PHASE 1)

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

3.1.3 EXPLORATORY OBJECTIVES FOR PARTS A AND B (PHASE 1)

- Evaluate the effect of JTX-2011 monotherapy (Part A) and JTX-2011 in combination with nivolumab (Part B) 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, and overall survival) of JTX-2011 as monotherapy (Part A) and in combination with nivolumab (Part B) in subjects with advanced 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, and progression free 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-2011with nivolumab (Safety/PK/Pharmacodynamics Expansion Cohorts AP1, AP2, BP1, BP2)

3.1.4 PRIMARY OBJECTIVES FOR PARTS C AND D (PHASE 2)

- Evaluate preliminary efficacy (response rate, duration of response, disease control rate, landmark progression free survival rate, progression free survival, landmark overall survival, and overall survival) of JTX-2011 as monotherapy (Part C) and in combination with nivolumab (Part D) in subjects with specific advanced solid tumor malignancies;
- Part C: Confirm the safety and tolerability of JTX-2011 monotherapy in five (5) expansion groups, including 4 cohorts with stratification for ICOS expression: C01- head and neck squamous cell carcinoma [HNSCC]; C02 - non-small cell lung cancer [NSCLC]; C03 - advanced refractory solid tumors other than those eligible for C01, C02, C04, or C05; and C04- gastric cancer; and 1 cohort without stratification: C05- MSI-H or dMMR endometrial cancer;
- Part D: Confirm the safety and tolerability of JTX-2011 in combination with nivolumab therapy in six (6) indication specific expansion groups, including 5 with stratification for ICOS expression: D01-HNSCC; D02-NSCLC; D03-triple negative breast cancer (TNBC); D04- melanoma; D05- gastric cancer; and 1 cohort without stratification: D06- MSI-H or dMMR endometrial cancer;
- Confirm the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D) of JTX-2011 monotherapy (Part C) and JTX-2011 in combination with nivolumab (Part D) in subjects with advanced solid tumor malignancies.

3.1.5 SECONDARY OBJECTIVES FOR PARTS C AND D (PHASE 2)

- Confirm the PK and Pharmacodynamics of JTX-2011 when administered as monotherapy (Part C) and in combination with nivolumab (Part D);

- Confirm the PK of nivolumab when administered in combination with JTX-2011 (Part D).

3.1.6 Exploratory Objectives for Parts C and D (Phase 2)

- 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, and overall survival);
- Evaluate the effect of JTX-2011 monotherapy (Part C) and JTX-2011 in combination with nivolumab (Part D) on peripheral blood immune cell markers and gene signatures.

3.1.7 Primary Objectives for Parts E and G (Phase 1)

- Assess the safety and tolerability of JTX-2011 in combination with ipilimumab therapy (Part E) and pembrolizumab (Part G) in subjects with advanced solid tumor malignancies after single and multiple ascending doses of JTX-2011

- Determine the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D) of JTX-2011 in combination with ipilimumab (Part E) and pembrolizumab (Part G) in subjects with advanced solid tumor malignancies.

3.1.8 Secondary Objectives for Parts E and G (Phase 1)

- Assess the PK and Pharmacodynamics of multiple ascending doses of JTX-2011 when administered as in combination with ipilimumab (Part E) and pembrolizumab (Part G).

- 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).

3.1.9 Exploratory Objectives for Parts E and G (Phase 1)

- Evaluate the effect of 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, and overall survival) of JTX-2011 in combination with

ipilimumab (Part E) and of JTX-2011 in combination with pembrolizumab (Part G) in subjects with advanced 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, and progression free survival).

3.2 STUDY ENDPOINTS

3.2.1 SAFETY ENDPOINTS

Assessment of safety and tolerability are primary objectives for both Phase 1 parts (A, B, E, G) and Phase 2 parts (C, D). Safety evaluations will include safety data throughout the duration of the study from enrolment to 28 days after last dose of study treatment using all available data. Safety will be characterized by System Organ Class (SOC) and Preferred Term (PT), frequency, relatedness to study treatment and severity of adverse events as coded using the MedDRA version 19 coding system and graded by NCI Common Toxicity Criteria for Adverse Events NCI CTCAE version 4.03. Safety endpoints also include laboratory values, vital signs, ECGs and Eastern Cooperative Oncology Group (ECOG) performance status.

Additional safety endpoints are described in section 3.2.5.1 and details of analyses and presentation will be included in the exploratory statistical analysis plan (eSAP).

3.2.2 PHARMACOKINETIC AND IMMUNOGENICITY ENDPOINTS

Assessment of PK are considered as secondary objectives for both Phase 1 parts (A, B, E, G) and Phase 2 parts (C, D). Endpoints will be the individual and summarized PK parameters from non-compartmental analysis (NCA). These parameters are listed and defined in Section 8.2.1 Pharmacokinetics.

Immunogenicity endpoints will include the incidence of anti-drug antibodies (ADA) to JTX-2011 and/or nivolumab, ipilimumab, or pembrolizumab and the incidence of neutralizing antibodies (NAb) to JTX-2011 and/or nivolumab, ipilimumab, or pembrolizumab.

3.2.3 EFFICACY ENDPOINTS

Efficacy evaluations are considered as primary objectives for Phase 2 parts (C, D) while for Phase 1 parts (A, B, E, G), efficacy evaluations are only considered as exploratory objectives. The efficacy endpoints will include the following:

- Objective Response Rate – Investigator Assessed and Central Review
- Immune-Related Objective Response Rate – Central Review
- Duration of Response – Investigator Assessed and Central Review

- Disease Control Rate – Investigator Assessed and Central Review
- Progression Free Survival (PFS) Time and Landmark PFS Rate – Investigator Assessed and Central Review
- Overall Survival (OS) and Landmark OS Rate

Detailed definition/derivation of each efficacy endpoints are provided in section 8.3.

3.2.4 PHARMACODYNAMIC ENDPOINTS

3.2.4.1 ICOS TARGET ENGAGEMENT ON CD4 T CELLS

ICOS target engagement on CD4 T cells is the primary pharmacodynamic biomarker in this study. Determination of the RP2D of JTX-2011 as monotherapy (Part A) or as part of a combination therapy (Part B, E or G) was a primary objective in Phase 1 parts (A, B, E, G) and confirmation of the RP2D of JTX-2011 as monotherapy (Part C) or as part of a combination therapy (Part D) was a primary objective in Phase 2 Parts (C, D). Evaluation of ICOS target engagement was the marker of pharmacodynamic activity on which selection and confirmation of the RP2D was based in this study.

3.2.4.2 JOUNCE PHARMACODYNAMIC BIOMARKER (JTXP)

JTXP was planned as a pharmacodynamic endpoint but will not be analyzed due to poor sample quality.

3.2.5 EXPLORATORY ENDPOINTS TO BE DOCUMENTED SEPARATELY

In addition to safety, PK, efficacy and pharmacodynamic endpoints included in sections above, additional exploratory endpoints are described in section 3.2.5.1 to 3.2.5.3. The details of the analyses and presentation of these exploratory endpoints will be included in a separate exploratory analysis plan.

3.2.5.1 SAFETY

The following safety exploratory endpoints will be assessed;

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

3.2.5.2 PHARMACODYNAMIC BIOMARKERS

- RNA analysis and changes in gene signatures (PBMC and tissue)
- Multiplex IHC for immune cell subsets pre/post to assess changes in T cell infiltrate in tumors (tissue)
- Immunophenotyping to assess effects on peripheral T cells (PBMC)
- Treatment-emergent ICOS hi CD4T cells (PBMCs) [not included in the protocol but added as an exploratory endpoint later]

3.2.5.3 POTENTIAL PREDICTIVE BIOMARKERS

The parameters listed below are categorized as potential predictive biomarkers. Samples will be run and results included in the analyses conditional on sufficient specimen availability. This list of endpoints includes but may not be limited to the following;

- ICOS expression by IHC (tissue)
- PD-L1 expression by IHC (tissue)
- ICOS RNA signature (tissue)
- DNA for mutational load and neoantigen (tissue)

Among the list above, only ICOS expression by IHC will be included in this main SAP while the rest will be included in the exploratory SAP. ICOS IHC is included in this SAP because enrollment in the study included stratification of subjects based on ICOS (IHC) assay results.

3.3 STATISTICAL HYPOTHESIS FOR EFFICACY

3.3.1 PRIMARY HYPOTHESIS

There is no formal hypothesis testing in either phase of this clinical trial protocol. The primary study endpoints of safety (for both Phase 1 and Phase 2) and the primary endpoints of efficacy (Phase 2) will be descriptively summarized for all study treatments and combinations.

3.3.2 MULTIPLE TESTING STRATEGY

Not applicable.

4. 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. Phase 1 portion of the study contains 4 parts (Part A, Part B, Part E, Part G) with all parts completed following protocol design. Phase 2 portion also contains 4 parts (Part C, Part D, Part F, and Part H) but Part F and H never opened up for enrollment.

The study plans to enroll approximately 498 evaluable subjects at approximately 36 sites in North America.

Parts A and B comprise dose escalations in subjects with advanced solid tumors to assess the safety and tolerability, identify the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D), and assess the PK and pharmacodynamics of JTX-

2011 alone and in combination with a fixed dose of nivolumab. Dose escalation scheme in Parts A and B follows the classical 3 + 3 design (more details in protocol section 6.2). Parts A and B also include expansion cohorts to collect additional safety, PK, and pharmacodynamics data in patients with ≥ 1+ ICOS expression levels (as determined by IHC) on archival tumor tissue or a history of documented PD1/PD-L1 expression.

Parts C and D evaluate the efficacy, safety, PK, pharmacodynamics and correlation of potential predictive biomarkers with efficacy. Part C is comprised of five (5) JTX-2011 single agent expansion cohorts to assess preliminary efficacy and confirm safety and tolerability, PK, and Pharmacodynamics in 3 indications expected to have higher levels of ICOS+ tumor-infiltrating T cells, namely HNSCC (C01), NSCLC (C02), and gastric cancer (C04), 1 cohort in other advanced solid tumors (C03), and 1 cohort of endometrial cancer with mismatch repair deficiency (dMMR) or microsatellite instability (MSI-H) (C05). Enrolment in Part C cohorts C01, C02, C03, and C04 is stratified for subjects with ICOS high tumors based on an IHC assay. Since MSI-H tumors may respond particularly well to immunotherapy, cohort C05 will not be stratified for ICOS. Part D is comprised of six (6) combination expansion cohorts; 5 in indications with anticipated higher levels of ICOS expression: HNSCC (D01), NSCLC (D02), triple negative breast cancer (TNBC) (D03), melanoma (D04), gastric cancer (D05), and 1 in dMMR or MSI-H endometrial cancer (D06). To ensure that a sufficient number of subjects with ICOS expressing T cells are enrolled to test the hypothesis that subjects with high levels of ICOS-expressing immune cells in the tumor will benefit most from ICOS agonist therapy, Part D Cohorts D01, D02, D03, D04, and D05 will also be stratified by expression of ICOS on tumor immune cell infiltrates. The IHC assay to be used for determining ICOS expression levels will be 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.

Parts E and G comprise dose escalations in patients with advanced solid tumors to assess the safety and tolerability, identify the MTD and RP2D, and assess the PK and pharmacodynamics of JTX-2011 in combination with a fixed dose of ipilimumab therapy (Part E) and JTX-2011 in combination with a fixed dose of pembrolizumab (Part G). Dose escalation scheme in Parts E and G follows the classical 3 + 3 design (more details in protocol section 6.2).

Study design and treatment cohorts are described in more details within the protocol section 5. Appendix 11.1 of this SAP shows a study design figure.

5. SAMPLE SIZE CONSIDERATIONS

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/Pharmacodynamics 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/Pharmacodynamics data. Subjects may also be added if exploration of intermediate dose level(s) of JTX2011 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). For Parts C and D, a group sequential design will be used to evaluate the preliminary efficacy of JTX-2011 or JTX-2011 in combination with nivolumab, with an interim look for futility. A 90% power at a 2-sided α will be achieved for the hypothesis testing by enrolling 15 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%.

6. ANALYSIS POPULATIONS

6.1 SAFETY ANALYSIS SET

The Safety Analysis Set (SAF) will be defined as those subjects who receive any portion of study drug (JTX-2011 and/or nivolumab and/or ipilumumab and/or pembrolizumab) where indicated. Subjects will include dose escalation and dose expansion portions of this clinical trial. Subjects will be identified as receiving study drug if the dose start date is completed on the electronic Case Report Form (eCRF). Subjects will be categorized to the planned dose group and actual dose received where actual is considered the initial/first dose received.

6.1.1 SUBSETS OF THE SAF

- Response Evaluable Set: subjects in SAF who have a baseline tumor assessment, and either has at least one post-baseline tumor assessment scan and/or discontinued treatment due to death or disease progression.
- The DLT Evaluable Set: SAF subjects in Phase 1 parts (A, B, E, G) who receive at least one dose of JTX-2011 during the DLT-evaluation period (1st cycle) and complete the DLT-evaluation period (1st cycle) or experience any DLTs.
- Biomarker Analysis Set: SAF who have a baseline sample and at least one post treatment biomarker sample.
- ADA Analysis Set: SAF who have a baseline sample and at least one post treatment ADA sample.

6.2 PHARMACOKINETIC ANALYSIS SET

The PK analysis Set will consist of all subjects with at least one quantifiable concentration data point for JTX-2011, nivolumab, pembrolizumab, or ipilimumab. Subjects in the PK analysis set with insufficient concentration data to calculate PK parameters will be included in the concentration data listings and summaries but excluded from the PK parameter listings and summaries.

6.3 TREATMENT MISALLOCATIONS

If subjects received the incorrect treatment(s) during the study, then the subjects will be reported under their planned treatment group for all efficacy analysis, but sensitivity analysis will be performed without these patients. For safety analysis, this subject will be reported under planned treatment group if less than half of the treatments were incorrect, otherwise will be reported under the actual treatment level.

7. GENERAL CONSIDERATIONS AND DATA HANDLING CONVENTIONS

7.1 FORMAT AND DISPLAY

All statistical analyses discussed in this SAP will be generated for the final CSR. All datasets, documentation, and the SAP will be archived in the Trial Master File (TMF). Tables, figures, and listings (TFLs), as described in this document and in the mock shells, will be created using SAS version 9.4 or higher. Mock table, listing, and figure shells will be developed for detailed presentation purposes. The mock tables, listings, and figure shells will not be considered as part of the SAP signoff.

TFL layout will be landscape. Margins will be a minimum as such: top 3/8 inch, bottom 3/8 inch, right 3/8 inch, and left 3/4 inch. Font will be a non-proportional courier new 8 or 9 pt font. Headers will include program name, associated project, and raw EDC data cut. Titles will generally have lines for Table/Figure/Appendix (i.e., Listing) with a number. Titles will include TFL numbers, where tables start with 14, listings with 16,

and figures with 14. Additional lines will include an appropriate title and study population for the output. All footnotes will be ordered by abbreviations, notes, and superscripted footnotes [1], [2], [3], etc. Report creation date and significant program modifications and date are documented in the SAS programs. At the bottom of each page a reference to the source data and the path of the program that created the TFL will be displayed. In some database systems, it is useful to extract a subset of data for use in the production of tables. The date of extraction printed will be the latest date upon which the extraction of contributing data occurred; which in some cases can come from multiple datasets. "Source data" refers to the data listings of SDTM or ADaM data appropriate for the TFL.

Database lock will be performed when all EDC and external data have been cleaned. The final database lock date will be considered the date of the final extraction dataset date (EDC or external).

7.2 STANDARD SUMMARY STATISTICS

Summary will be provided separately for each Phase 1 part (A, B, E, G) by dose level and for each Phase 2 part (C, D) by tumor type cohort unless specified otherwise. A total column will also be provided in summary tables as appropriate. Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be calculated for all continuous variables. Geometric mean, geometric coefficient of variation (GCV%), interquartile range (IQR:Q1-Q3) and 2 sided confidence intervals may also be presented as appropriate. For continuous parameters, the sample number will be displayed as a whole number. In general means and medians will be reported to one additional decimal place as compared to original data as collected and standard deviation will be reported to 2 additional decimal places. Minimums and maximums will be reported as collected. Data will be aligned by decimal place where appropriate. Column headers will have (N=) where applicable.

Frequencies and percentages will be presented for categorical and ordinal variables. Frequencies are not displayed for counts of zero. All frequency counts greater than 0 will have percentages displayed. Count and percentages will be displayed in the form xxx (xxx.x). All percentage columns will be right justified. Column headers will have (N=) and where applicable n (%).

7.3 BASELINE VALUE AND CHANGE FROM BASELINE

Unless otherwise specified, baseline values are defined as the most recent non-missing value obtained immediately prior to administration of first dose of study treatment and within 28 days prior to first dose. Change from baseline will be calculated by subtracting the baseline value from the post-dose assessment for each subject (i.e. post-dose minus baseline).

7.4 STUDY DAY

The first day of treatment will be designated as Study Day 1, which is also Cycle 1 Day 1 (C1D1). The day prior to the first day of treatment is Study Day-1, two days prior is Study Day -2, etc. Baseline or pre-treatment day/week/month/year calculations will be performed as date from first dose date minus closest date to first dose date, whereas post-baseline day/week/month/year calculations will be date from first dose date minus closest date to first dose date plus 1.

7.5 STANDARD DATE/DAY CONVERSION AND MISSING DATE CONSIDERATIONS

Dates will be formatted as YYYY-MM-DD (ISO-8601 Standard). For the purpose of converting days to years or months, one year = 365.25 days and one month = 30.4375 days.

7.5.1 MISSING DATES AND STUDY DAY DERIVATION

Dates missing the day, month, or year will be formatted to the following:

- If the eCRF has date fields for day, month, and year
  - Full date format: YYYY-MM-DD
  - Missing day: YYYY-MM
  - Missing day & month: YYYY
- If the eCRF has date fields for month and year
  - Full date format: YYYY-MM
  - Missing month: YYYY
- If the eCRF has date fields for year
  - Full date format: YYYY

Missing day, month, and year should be displayed with a dash "-" for each character value missing so that it is known to be missing rather than a potential programming error. If options of "UNK=Unknown", "ND=Not Done", "NA=Not Applicable", or "NS=Not Specified or No Sample" are indicated on the eCRF the acronyms should be included for their respective missing information. For the purposes of a listing, dates should reflect only the information provided by the investigator.

The study day derivation for missing or partially missing dates for purposes of calculations will be as follows:

- Missing start date (day) only: Impute with 01, unless data collected in other domains provide a reasonable timeframe of which the day can be inferred. Basis of day selection should be properly described in the program.

- Missing start date (month and day) only: Impute month as 01 and day as 01, unless data collected in other domains provide a reasonable timeframe of which the day can be inferred. Basis of day selection should be properly described in the program.

- Missing stop date (day) only: Impute with 30 or 31 (end of the month), unless data collected in other domains provide a reasonable timeframe of which the day can be inferred. Basis of day selection should be properly described in the program.

- Missing stop date (month and day) only: Impute month as 01 and day as 31, unless data collected in other domains provide a reasonable timeframe of which the day can be inferred. Basis of day selection should be properly described in the program.

For adverse events, if the subject died and AE stop date is missing, the date of death is assigned. Missing stop dates for ongoing adverse events are assigned to whatever is the maximum date between treatment discontinuation date, study discontinuation date, visit date, or onset date. If the subject does not record a date of discontinuation, the stop date is the maximum of onset date or visit date.

7.6 Visit Windowing

Assessments that do not have cycle and day/visit allocated or pre-specified in the datasets will be assigned to cycles based on the collection date of the sample relative to the start dates of the cycles from the study drug administration page.

7.7 Central Review and Assessment

Central review will be done in a blinded and independent manner by two image evaluators (readers). Where there is non-agreement between the two response evaluations, a third party adjudicator will indicate which evaluation will be considered in the analysis.

7.8 Laboratory Data Conversions

7.8.1 General

All laboratory data will be displayed as recorded on the eCRF. Laboratory values collected as a range may be converted to numeric values when evaluating abnormalities, but should not be included in calculations of change from baseline.

Data collected as inequalities (e.g., >5, <5, >= 5) will be converted to numeric values for evaluating abnormalities but will not be included in summarizations or descriptive displays such as change from baseline. Data using the form of ">5" or "<5" are converted to numeric by adding or subtracting a "fuzz factor" 0.001 (e.g., <5 should be

4.999 and >5 should be 5.001). Data using the form "<=" or ">=" will be converted to the numeric value (e.g., <=5 should be 5). Reference ranges that are recorded as a less than value (e.g., <10) should be placed in the database as a zero to that value (e.g., 0 – 10).

7.8.2 CONVERTING RANGE DATA TO NUMERIC

1. Determine that the LABVALUE is composed of two numeric words separated by a hyphen or blanks and a hyphen.
2. Establish the range as the highest and lowest values.
3. Test that the first value in the range is less than or equal to the second. If not, output an error message and set the numeric output variable to a SAS missing value.
4. The numbers resulting from a textual conversion, the reference limits, and the lower and upper abnormality limits are rounded using a "fuzz factor." This eliminates digits that could cause two values to compare unequally due to rounding errors made by the computer.
5. If both lower and upper range values are within the normal limits, then assign the midpoint of the lower and upper range values to the numeric lab test result variable.
6. If the lower range value is below the lower limit of normal, but the upper range value is within the normal limits, then assign the lower range value to the numeric lab test result variable.
7. If the upper range value is above the upper limit of normal, but the lower range value is within the normal limits, then assign the upper range value to the numeric lab test result variable.
8. If the lower range value is below the lower limit of normal and the upper range value is above the upper limit of normal then an error condition exist. The range in the text lab value should not span the normal limits.

7.8.3 DIFFERENTIALS

Hematology results include neutrophils, lymphocytes and eosinophils recorded as absolute cell counts and/or percent of the white blood cell counts. For summarization purposes, percent values may be converted to absolutes by multiplying the percent value by the white blood cell count at the same time point. ~~Listings will display the original values.~~

7.9 EXAMINATION OF SUBGROUPS

Subgroup analysis will be described in section 9 of the SAP.

7.10 STATISTICAL COMPARISON METHODS

No comparisons will be made.

7.11 Statistical Significance

Not applicable

7.12 Missing Data

7.12.1 Imputation of Non-Date Missing Data for Statistical Analyses

Unless otherwise explicitly specified, missing data will not be imputed. All available time to progression or death data will be analysed using appropriate statistical methods that allow for censoring when no progression or death is reported. Subjects with reported shorter treatment and/or follow-up intervals will not be considered to have missing time to progression or death status. Subjects with premature study withdrawal (including lost to follow-up) will be included in any analyses where they contribute data and where they conform to the analysis population of interest.

Subjects without baseline tumor assessments will be considered non-evaluable for ORR and irORR analysis.

When using RECIST v1.1 or irRC criteria to estimate the proportion of responders, all subjects in Response Evaluable Set will be included in the denominator even when their responses are missing.

7.12.2 Handling of Missing and Non-Quantifiable Data for Pharmacokinetic Analyses

Concentration data will be considered missing if:

- No sample is collected
- A sample is collected but no valid bioanalytical data are reported for any reason

Missing values will be considered missing for the purposes of listing, summarization and analysis, with the exception that Cycle 1 Day 1 pre-dose concentrations will be set to "0" if missing for the purposes of NCA analysis.

If a sample is collected and analysed, but is of questionable identity due to possible sample handling or labelling errors either at the clinical site or the bioanalytical lab, the concentration will be reported and flagged in the listings, and the rationale for considering the identity questionable will be documented. The data will be set as missing in the primary NCA analysis and statistical summarization, but a sensitivity analysis may be conducted in which the concentration data point is included in the NCA and statistical summarization for NCA results for the relevant Dose and Cycle repeated.

If a quantifiable concentration is available but the actual sampling time is missing, the nominal sampling time will be used.

Bioanalytical data that are below the limit of quantitation (BLQ) will be treated as follows:

- For listings, BLQ will be reported as "< LLQ" (lower limit of quantitation)
- For NCA, BLQ concentrations will be set to 0

8. ENDPOINT DEFINITIONS AND DERIVATIONS

8.1 SAFETY DEFINITIONS AND ENDPOINTS

8.1.1 ADVERSE EVENT ENDPOINTS

Adverse events will be categorized by pre-existing, treatment emergent and post treatment.

- Pre-existing AEs are designated to events that occur prior to the first dose of study drug(s) or observed prior to first dose but did not increase in NCI CTCAE toxicity grade during treatment period.

- Post-treatment adverse events will be any adverse events reported outside the 28 day post dose treatment window until the end of study participation. Any subsequent non-protocol treatment for the cancer diagnosis will end the potential study drug(s) adverse event data collection.

- Treatment-Emergent Adverse Events (TEAEs) are designated to events that occur after the start of study drug(s) and on or before 28 days after final dose of study drug, and were not observed prior to start of treatment; Or if the event was observed prior to the start of study drug but increased in NCI CTCAE grade after either the start of study drug or prior to 28 days after the final dose of study drug. Pre-existing adverse events may be reclassified as TEAEs if the frequency of the event increases during treatment.

- Treatment Related TEAEs will include those TEAEs which are possibly or probably related to study drug(s) as designated by the investigator. Events having a missing relatedness will be designated as definitely related on tables but the listing will display the data as collected. Relationship may be attributed by JTX-2011 and/or nivolumab/ipilimumab/pembrolizumab and will be displayed separately.

- Serious adverse events (SAEs) will include all events classified as serious on the eCRF. The electronic database used to enter data at the site (i.e., RAVE / iMedidata) will be deemed as the complete report for adverse event information. The pharmacovigilance database will be reconciled against the EDC.

- Infusion related reactions (IRRs) may be captured as an adverse event as well as the symptoms that cause the IRR. Symptoms of IRRs are events occurring shortly after or during the study drug infusion. Symptoms may include but are not limited to: flushing, headache, nausea, fever, chills, dyspnea, rash, hypotension, wheezing, coughing, tachycardia. Any sign/symptom determined to be associated with an IRR may be counted as such in adverse event reporting. The highest grade sign/symptom must be associated with the IRR preferred term.

- Immune-related adverse reactions (irAEs) are unique side effects typically seen after dosing with checkpoint inhibitors. At a minimum, the following have been associated with irAEs and will be evaluated for incidence in the combination arms: pneumonitis, colitis, hepatitis, endocrinopathies (hypophysitis), adrenal insufficiency, hypothyroidism and hyperthyroidism, type I diabetes mellitus, nephritis (defined as renal dysfunction or >=G2 increased creatinine requiring corticosteroids), rash, encephalitis (neurologic signs/symptoms), others include: motor dysfunction, vasculitis, myasthenic syndrome. Some ipilimumab associated irAEs include but are not limited to: uveitis, iritis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barre syndrome, hypopituitarism, system inflammatory response syndrome, gastritis, duodenitis, and sarcoidosis.

8.2 Pharmacokinetics and Immunogenicity Definitions and Endpoints

8.2.1 Pharmacokinetics

PK will be evaluated by non-compartmental analysis (NCA). The table below defines the PK parameters that maybe derived from the NCA for this study.

Parameter Abbreviation	Definition	Unit	Dependence on λ_z
C_{max}	Maximum observed plasma concentration	ng/mL	no
T_{max}	Time when C_{max} is observed	days	no
AUC_{last}	Area under the drug concentration-time curve from time 0 to the time of the last quantifiable drug concentration	ng·days/mL	no
AUC_{inf}	Area under drug concentration curve from time 0 extrapolated to infinity	ng·days/mL	yes
λ_z	Terminal elimination rate constant	$days^{-1}$	NA
$t_{1/2}$	Terminal elimination half-life	days	yes
CL	Clearance of drug	L/day	yes
V_d	Volume of distribution	L	yes
C_{max}/D	C_{max} normalized by dose	ng/mL/mg	no

AUC_{last}/D	AUC_{last} normalized by dose	ng·days/mL/ mg	no
AUC_{inf}/D	AUC_{inf} normalized by dose	ng·days/mL/ mg	yes

Parameters with no dependence on λ_z will be calculated for all subjects. Parameters with a dependence on λ_z will be calculated and reported as described in Section 9.10 Pharmacokinetic and Immunogenicity Analyses.

8.2.2 IMMUNOGENICITY

Immunogenicity endpoints include ADA and NAb incidence.

8.3 EFFICACY DEFINITIONS AND ENDPOINTS

8.3.1 RECISTv1.1

For solid tumors, investigators will evaluate the size of the tumor based on a set of published guidelines called Response Evaluation Criteria in Solid Tumors (RECIST). The current set of guidelines are referred to as RECISTv1.1 (Eisenhauer, et al., 2009). Tumor evaluations are based on Target and Non-Target lesions plus new lesions potentially occurring post dose at subsequent assessments.

Measurable lesions will include nodal and non-nodal as follows: 1) lesions with longest diameter 10mm or greater in the axial plane when assessed by CT or MRI, 2) lesions with the longest diameter at least 20 mm with assessed by chest x-ray 3) superficial lesions with longest diameter 10 mm or greater when assessed by caliper 4) malignant lymph nodes with the short axis 15 mm or greater when assessed by CT. RECIST recommends contiguous slice thickness of less than or equal to 5mm for CT or MRI. Nodes with a short axis less than 10mm should not be considered malignant lesions. Ultrasound is not suitable for tumor assessment.

Non-measurable lesion categorization will include all other diseases including lesions too small to be considered measurable, pleural or pericardial effusions, ascites, bone disease, inflammatory breast disease, leptomeningeal disease, lymphangitis, pulmonitis, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging, nodes with short axis greater than or equal to 10mm but less than 15mm, disease documented by indirect evidence only (e.g., lab values) or previously radiated lesions that have not progressed.

Target lesions are defined as all measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs and should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (lesions with longest diameter for non-lymph nodes and nodes with longest short axis ≥15mm)

and suitability for accurate repeated measurements. Measurements are recorded in mm and must be provided for target lesions.

Non-target lesions may include non-measurable disease lesions and measurable lesions not identified as target lesions. Absent, indeterminate, present/not increased or increased are the evaluation codes for non-target disease assessment.

Inadequate tumor assessment does not allow for a RECIST response determination and will be designated as Not Evaluable target response evaluation. An inadequate assessment will be defined as those with at least 1 missing measurement or non-measurable target lesion or baseline tumor assessment outside the screening evaluation window (i.e., after first dose date, prior to -28 days from first dose date). If a target lesion is too small to measure and does not have unequivocal complete disappearance, a default of 5mm will be assigned.

Different imaging of lesions should not be performed. Imaging variations that result in PR or CR based on the inconsistency of imaging will be reviewed carefully and may result in adjudication. Response is assessed in EDC by investigators with documented (objective) status at each assessment.

Objective review of tumor assessment scans will be performed using both investigator assessments and central review. Central review will be generated per an imaging service charter. Central review will be conducted independently of investigator assessment responses.

Table 1 Definitions of Target and Non-Target Response per RECIST version 1.1

Objective Response	Target Lesions	Non-Target Lesions
Complete Response (CR)	Disappearance of all target lesions. All pathological lymph nodes must have decreased to < 10 mm on the short axis.	Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (i.e., <10 mm short axis). Normalization of tumor marker levels
Partial Response (PR)	At least a 30% decrease in the sum of the longest diameters (SLD) of the target lesions, taking the baseline SLD as reference.	Not Applicable
Non-CR / Non-PD	Not Applicable	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Objective Response	Target Lesions	Non-Target Lesions
Stable Disease (SD)	Neither sufficient shrinkage to qualify as a PR nor an increase for PD.	Not Applicable
Progressive Disease (PD)	SLD increased by at least 20% from the smallest value on study (including baseline, if that is smallest). The SLD must also demonstrate an absolute increase of at least 5 mm.	Unequivocal progression of existing non-target lesions.
Not Evaluable (NE)	Progression not documented and • ≥ 1 target lesion not assessed, or • assessment methods inconsistent from baseline, or • ≥ 1 target lesions cannot be measured accurately (poor visibility) • ≥ 1 target lesions were excised or irradicated and have not reappeared or increased	Progression has not been determined and ≥ 1 non-target lesions were not assessed or were inconsistent with those used at baseline
Not Applicable (NA)	set value for all post-baseline disease assessments only if no target lesions are identified at baseline	set value for all post-baseline disease assessments only if no non-target lesions are identified at baseline

Table 2 Response Evaluation per RECIST version 1.1

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR or NA	No	CR
CR	Non-CR/Non-PD or NE	No (or NE)	PR
PR	CR or Non-CR/Non-PD or NE or NA	No (or NE)	PR
SD	CR or Non-CR/Non-PD or NE or NA	No (or NE)	SD
PD	Any	Any	PD
Any	PD	Any	PD
Any	Any	Yes	PD
NE	CR or Non-CR/Non-PD or NE or NA	No	NE
NA	CR	No	CR
NA	Non-CR/Non-PD	No	SD

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
NA	NE or NA	No (or NE)	NE
NA	CR or Non-CR/Non-PD	NE	SD

8.3.2 Objective Response Rate – Investigator Assessed and Central Review

Objective response rate (ORR) is defined as the proportion of subjects with a Best Overall Response (BOR) characterized as either a Complete Response (CR) or Partial Response (PR) as defined by RECISTv1.1 guidelines, relative to the total number of evaluable subjects in the population of interest. Per RECISTv1.1 guidelines, subjects with documented PR or CR will need confirmatory tumor assessments to document tumor response. Subjects without baseline tumor assessments will be considered non-evaluable for this analysis. Responses are only considered if they occur prior to objective progression and the start of subsequent anticancer therapy.

8.3.3 Best Overall Response – Investigator Assessed and Central Review

Best overall response is defined as the best response (in the order of CR, PR, SD, PD, and NE) among all overall responses recorded from the first dose date until documented PD, or the last evaluable disease assessment in the absence of PD prior to the initiation of subsequent anticancer therapy or end of the study, whichever occurs first. Best Overall Response (BOR) is based on RECIST v1.1 criteria. Subjects with documented PR or CR will need confirmatory tumor assessments to document response (refer to Table 3). If a CR is pending confirmation and is designated at an assessment followed by 1 or more NE, CR may be confirmed thereafter. Similarly, if a PR is pending confirmation and is designated at an assessment followed by 1 or more NE and/or SD assessments, PR may be confirmed thereafter.

Table 3 Best Overall Response

Overall Response First Time Point	Overall Response Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD or PR [1]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

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

8.3.3.1 Confirmed Overall Response

Confirmed overall response is defined as subjects with a best overall response of confirmed CR or confirmed PR that occur prior to the initiation of subsequent anticancer treatment or prior to discontinuation of treatment (due to any other reason),whichever is earlier.

8.3.4 Disease Control Rate – Investigator Assessed and Central Review

Disease control rate (DCR) is defined as the ratio of subjects having any of the following response:

- Confirmed CR or PR; Or
- BOR of SD (or unconfirmed CR or PR) lasting at least 53 days (9 weeks less 10 days) from date of first dose.

Note that a SD at the first scan requires a follow-up scan of SD or better (PR or CR) along with the timeframe requirement. Unconfirmed responses will be considered SD at study completion.

8.3.5 PROGRESSION-FREE SURVIVAL – INVESTIGATOR ASSESSED AND CENTRAL REVIEW

The investigator will make tumor assessments and a separate independent central review will also be performed. All PFS calculations (months) will be the following:

[Progression/Death/Censor Date – First Dose Date + 1] / 30.4375.

PFS is defined as the number of months from the date of first dose to the date of death or documented (objective) disease progression via RECISTv1.1, whichever occurs earliest. Subjects that do not experience progression or death at the time of analysis will have time to progression censored at the date of last valid tumor assessment, which is defined as an overall response other than "not evaluable". The actual tumor assessment date (i.e., scan) will be used, not the reading date of the scan/assessment. If the tumor assessment is performed over multiple days for a documented disease progression, the first date will define the assessment date. If the subject is censored, the last date will define the assessment date. Again the "assessment date" will be defined as the "scan date" and not the overall response date. Tumor assessments are performed within 10 days prior to every 3rd cycle starting from cycle 4 (e.g., C4, C7, C10, etc.) until treatment discontinuation. 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.

8.3.5.1 LANDMARK PROGRESSION FREE SURVIVAL RATE

Landmark Progression Free survival will be estimated at 6 months and 12 months, where applicable. Landmark analysis is one of most commonly used approaches for the analysis of these kinds of time-dependent covariates in time-to-event data. It considers responses up to and including a fixed landmark timepoint. The PFS rate at 6 and 12 months is the

number of subjects who did not progress and were alive at the 6 or 12 month timepoint over the number of subjects considered as evaluable and is displayed as a percentage.

8.3.5.2 CENSORSHIP

In general, subjects are censored at the date of the last objective disease assessment that verified lack of disease progression if they are last known to be alive, on-treatment or within 28 days following treatment discontinuation, and progression-free. Censoring is explicitly described below:

- Subjects with inadequate/incomplete baseline disease assessment will be censored at the first dose date.
- Subjects not reassessed after first dose date will be censored at the date of first dose date unless death occurred prior to the first planned assessment (in which case the death is an event).
- Subjects with at least one on-study disease assessment who discontinue treatment without documented disease progression or death are censored at the date of the last objective disease assessment documenting no progression.

There are two exceptions:

- If objective progression or death is documented ≤ 28 days after discontinuation then progression or death is an event
- If a new anti-cancer treatment is started prior to objective progression and ≤ 28 days after discontinuation, then censorship is at the date of the last objective disease assessment that verified lack of disease progression prior to the new treatment

Subjects with documentation of progression or death after an unacceptably long interval (i.e., 2 or more missed or indeterminate/not evaluable assessments) since the last tumor assessment will be censored at the time of last objective assessment documenting no progression.

Table 4 Evaluation of Radiographic Disease Progression and Censoring

Situation	Date of	Outcome
Inadequate baseline tumor assessment	First Dose Date	Censored
No post-baseline assessment and no death prior to first scheduled assessment		
Death or documented PD after ≥ 2 consecutively missed and/or not evaluable scheduled tumor assessments	Last tumor assessment documenting no PD	
Alive, on-treatment, and no documented PD	Last tumor assessment documenting no PD	
Documented PD (on, prior to, or ≤ 28 days after treatment discontinuation)	First tumor assessment documenting PD	Progression (Event)

New anticancer treatment prior to PD	Last tumor assessment documenting no PD prior to new anticancer treatment	Censored
Treatment discontinuation due to toxicity, undocumented progression, or other reason	Last tumor assessment documenting no PD prior to discontinuation	Censored
Death prior to first scheduled assessment	Death	Death (Event)
Death without documented PD and ≤ 28 days after treatment discontinuation	Death	Death (Event)

8.3.6 DURATION OF RESPONSE – INVESTIGATOR ASSESSED AND CENTRAL REVIEW

Duration of response (DOR) is defined as the interval of time between date of first documented response (CR or PR with caveat of confirmation) to the earliest date of disease progression or death due to any cause, whichever occurs first. Censorship will be determined using the definitions in Section 8.3.5.2. DOR will be calculated for the subgroup of responder subjects.

[Progression/Death/Censor Date – Date of First Response + 1] / 30.4375.

8.3.7 OVERALL SURVIVAL

Overall survival (OS) is defined as the interval of time from first dose date to the date of death for any cause. In the absence of confirmation of death, survival time will be censored at the last date the subject is known to be alive. OS calculations (months) will be the following:

[Death/Censor Date – First Dose Date + 1] / 30.4375.

8.3.7.1 LANDMARK OVERALL SURVIVAL RATE

Landmark Overall Survival will be estimated at 6 months and 12 months, where applicable. The OS rate at 6 and 12 months is defined as the number of subjects who were alive at the 6 or 12 month timepoint over the number of subjects considered as evaluable and is displayed as a percentage.

8.3.8 IMMUNE-RELATED RESPONSE CRITERIA

Immune-related Response Criteria (irRC) as outlined below is based on/defined in the Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria (Wolchok et al., 2009).

Table 5 Definitions of Response per irRC

Immune-Related Response	Definition by Timepoint
Complete Response (irCR)	Complete disappearance of all lesions (whether measurable or not, and no new lesions) Need confirmation by a repeat, consecutive assessment at least 4 weeks from the date first documented
Partial Response (irPR)	At least a 50% decrease in decrease in tumor burden (sum of the product of perpendicular diameters (SPD) of measurable lesions) relative to baseline Need confirmation by a consecutive assessment at least 4 weeks after first documentation
Stable Disease (irSD)	Not meeting criteria for irCR or irPR, in absence of irPD
Progressive Disease (irPD)	At least a 25% increase in tumor burden (SPD of measurable lesions) relative to nadir (minimum recorded tumor burden) Need confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented

8.3.9 Immune-related Objective Response Rate – Central Review

Immune-related best overall response (irBOR) will only be evaluated according to central review. The irBOR (as defined by irRC guidelines) is recorded from first dose date until documented disease progression (irPD) or death . The irORR is defined as the proportion of subjects with an irBOR characterized as either a confirmed complete response (irCR) or confirmed partial response (irPR) prior to the initiation of subsequent anticancer treatment or prior to discontinuation of treatment (due to any other reason),whichever is earlier; irORR will be calculated relative to the total number of evaluable subjects. Subjects without baseline tumor assessments will be considered non-evaluable for this analysis.

8.4 Pharmacodynamic Endpoint

8.4.1 ICOS target engagement

ICOS target engagement on CD4 T cells is considered as a primary pharmacodynamic endpoint for both Phase 1 and Phase 2.

ICOS target engagement is measured by a receptor occupancy assay in peripheral blood mononuclear cells collected pre-treatment and at multiple time points on study. The baseline pre-treatment sample is considered to have 100% ICOS available, and all subsequent timepoints are reported as a % of the baseline ICOS score. Target engagement will be used to select the dose for safety/PK/Pharmacodynamics expansion cohorts AP1, AP2, BP1, BP2, and the RP2D.

8.4.2 Predictive Biomarker Endpoints

8.4.2.1 ICOS Expression by IHC

Tumor biopsy samples may be available for each subject in two ways; as an archived sample and or as a fresh (in study pre-treatment) sample. Biopsies will be analysed by Neogenomics using a validated assay to estimate the percentage of ICOS expressing immune cells in the sample. Where the percentage of cells is less than 1%, the ICOS IHC score will be set to 0. Where the percentage is greater than or equal to 1% and less than 5%, the ICOS IHC score will be set to 1. Where the percentage is greater than or equal to 5% and less than 15%, the ICOS IHC score will be set to 2 and where the percentage is 15% or greater, the ICOS IHC score will be set to 3. Missing ICOS values will not be classified.

ICOS high/low subgroups will be determined using the Neogenomics data as described above, with ICOS high subgroups represented by ICOS IHC score of 2 or 3 and ICOS low subgroups represented by ICOS IHC score of 0 or 1. ICOS subgroups may also be formed by grouping ICOS IHC score of 1, 2, and 3 together and using ICOS 0 as a separate subgroup. Missing ICOS values will not be imputed and any analysis using these will have the category ICOS high/low missing. Please refer to section 9.11.5 for subgroup analysis.

9. STATISTICAL ANALYSIS AND METHODOLOGY

9.1 Disposition of Subjects

Frequency of patients enrolled, allocation to analysis populations and distribution by site will be tabulated. Frequencies and percentages of subject's treatment and study participation and final disposition will be reported overall and by site. Deaths while on-treatment (28 days post last dose, or start date of new anti-cancer drug therapy - 1, whichever is earlier) and off-treatment will be counted. Reason for end of treatment and end of study reasons will be summarized. Protocol deviations will be listed and major protocol deviations will be summarized.

9.2 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized:

- Continuous variables: Age [years], weight [kg], height, body mass index [kg/m^2], duration of disease since first diagnosis (at time of screening) [months], time since last anti-cancer treatment prior to study enrollment [months].

- Categorical variables: Age group [≤50, 50 to ≤ 65, >65], gender, race, ethnicity, ECOG performance status [0/1/2/3/4/5], smoking status [Never/Current/Former], prior IO therapy [Yes/No], prior IO refractory status [Yes/No], Prior PD-1 or PD-L1 therapy [Yes/No], ICOS IHC score in archived sample and fresh sample [0/1/2/3/NE], histological subtype, Total Proportion Score (TPS) ≥1% [Yes/No], TPS ≥50% [Yes/No], Combined Positive Score (CPS) ≥1% [Yes/No] and CPS ≥10% [Yes/No] for archival tumor samples.

9.3 MEDICAL HISTORY

Medical history summaries will include tumor type at primary diagnosis and medical history by SOC and PT. Prior surgeries by type and location will be summarized. Baseline tumor assessment and disease sites will also be summarized. Data will be provided in subject listings.

9.4 PRIOR THERAPY

Prior systemic lines of therapy and prior immunotherapies will be summarized using data as collected in the eCRF. The following will be summarized categorically for each unless stated as a continuous parameter.

- Number and type of prior systemic therapies and prior best response

- Number and type of prior immunotherapies

Medical review will be used determine the assignment of prior anti-cancer treatment categories and regimen. The final list of this determination will be maintained in the trial master file and signed by the study Medical Director.

Data as collected in eCRF will be provided in subject listings.

9.5 RADIOTHERAPY

Prior radiotherapy will be summarized using data as collected in the eCRF. The following will be summarized categorically unless stated as a continuous parameter.

- Location of radiotherapy by body site

- Average total dose (by unit) as recorded by body site

9.6 CONCOMITANT MEDICATION

Concomitant Medications will be summarized by ATC and PT using WHO Drug Version SEP2016. Prior and concomitant medications will be listed.

9.7 DURATION OF TREATMENT AND IN-STUDY PARTICIPATION

Subject participation will be summarized using descriptive statistics. Intervals are defined as follows; first dose of study drug to end of study treatment, first dose of study drug to end of study participation and first dose of study drug to death, when reported.

9.8 STUDY DRUG EXPOSURE AND DOSING

9.8.1 EXPOSURE TO STUDY DRUG

Extent of treatment exposure will be summarized for JTX-2011 and JTX-2011 and nivolumab /or ipilumumab /or pembrolizumab as follows:

- Total Exposure (weeks) derived as (last dose date – first dose date + 1)/7
- Number and percentage of patients beginning 1, 2, 3, …., 6 and > 6 cycles [Actual dose groups] and number of cycles started summarized as a continuous variable
- Total actual cumulative dose (mg/kg) received overall and by cycle, where total actual dose is the summation of each dose as collected on the eCRF

9.8.2 SUMMARIZATION OF DOSE INTERRUPTIONS AND DOSE MODIFICATIONS

A dose reduction is defined as when the actual dose administered is less than the prescribed dose (within 10% is not considered a reduction) on any given day for any reason with the exception of a day where the total dose administered is 0 mg as this is not considered a dose reduction.

A dose interruptions/delay/missed dose is defined as a planned dosing day with 0 mg administered.

Subjects will be summarized by total number of doses, subject frequency of doses and percentage according to:

- Patients with at least one dose reduction overall and by cycle.
- Patients with at least one dose interruption overall and by cycle

Subjects having a dose interruption or dose reduction due to an adverse event will be listed.

9.8.3 DOSE INTENSITY SUMMARIZATION

Study drug administration will be summarized as follows: Number of doses received, cumulative dose in mg, treatment duration in weeks, dose intensity in mg/week and relative dose intensity (%).

Dose intensity (mg/week) and relative dose intensity (%) is calculated as follows

$$\text{Dose Intensity (mg/week)} = \frac{\text{Cumulative Dose (mg)}}{\text{Treatment Duration (weeks)}}$$

$$\text{Relative Dose Intensity (\%)} = \frac{\text{100*Dose Intensity (mg/week)}}{\text{Planned Dose Intensity (mg/week)}}$$

where

$$\text{Planned Dose Intensity} = \frac{\text{Planned Dose (mg) per cycle*total \# cycles}}{\text{(Planned days in cycles*total\# cycles)/7}}$$

Data will be provided in subject listings.

9.9 SAFETY ANALYSES

The safety analysis will include the evaluation of the following data:

- Adverse events (AEs)
- Laboratory results
- Vital signs: pulse rate, systolic and diastolic blood pressure
- Electrocardiograms (ECGs)
- Physical exams
- ECOG

All safety parameters will be summarized descriptively. The SAF will be used for displaying safety outputs unless otherwise specified. Subsets of the safety set may be presented separately. Data will be provided in subject listings.

9.9.1 ADVERSE EVENTS

Adverse events (AEs) will be listed and summarized using MedDRA v19 coded terms. Listings will be created by categories for AEs as outlined below:

- All adverse events (AEs) with flags for treatment emergent adverse events (TEAEs) and flags of relatedness to study drug(s)
- SAEs with flags for treatment emergent adverse events (TEAEs) and flags of relatedness to study drug(s)
- Immune related adverse events (irAEs)
- Infusion related reactions (IRRs)
- TEAEs leading to death
- TEAEs leading to study drug interruption, reduction, hold or permanent study drug discontinuation
- TEAEs considered as DLTs

A general overview summary table will include frequencies by category of AE (as listed above) and will also include TEAE by severity grade and relationship to study drug (both JTX-2011 and/or nivolumab and/or ipilumumab and/or pembrolizumab).

Frequencies and percentages will be reported by System Organ Class (SOC) and Preferred Term (PT). Patients with multiple events for a category will be counted once in the highest CTCAE classification. Summary tables will include treatment-emergent AEs, unless specified otherwise. Missing onset date for an event will be considered as TEAE. If relatedness is missing the adverse event will be considered related. The denominator (N) for adverse events reported at each cycle will include SAF patients who are dosed at least once in that cycle. Important note: Patients will be counted in terms of number and adverse event in the actual dose group as received, not the as intended dose group. Summary tables by SOC and PT will be sorted in descending frequency of SOC for the total column, then in descending frequency of PT within SOC for the total column. Summary tables by PT will be sorted in descending frequency of PT for the total column.

The following summary TEAE tables listed in Table 7 below will be presented for Phase 1 and Phase 2 parts. In addition, DLTs will be summarized by SOC and PT only for Phase 1 parts (A, B, E, G) for DLT Evaluable Set.

Table 7 Summary of Adverse Event Displays

Category	TEAE	IRR	irAE	TEAE Related to JTX2011	TEAE Related to Any Study Drug	Serious TEAE	Related SAE	TEAE Resulting in Death	TEAE Resulting in Dose Interruption, Reduction or Hold	TEAE Resulting in Study Drug Discontinuation
SOC and PT	X			X	X	X	X			
SOC/PT/Max. Grade	X			X	X					
SOC/PT/Max. Grade ≥=3				X						
SOC/PT by Cycle	X									
SOC/PT by Grade, Cycle										

Category	TEAE	IRR	irAE	TEAE Related to JTX2011	TEAE Related to Any Study Drug	Serious TEAE	Related SAE	TEAE Resulting in Death	TEAE Resulting in Dose Interruption , Reduction or Hold	TEAE Resulting in Study Drug Discontinuation
PT	X	X	X	X		X	X	X	X	X
PT and Cycle		X	X							

A patient having multiple events within a system organ class is counted only once for that SOC. Similarly, a patient having multiple events under a preferred term is counted only once for that PT.

9.9.2 Laboratory Data

Laboratory parameters will be analyzed using categorical summaries.

Categorical analysis of laboratory tests using observed data includes summarizing laboratory abnormalities considered clinically significant and treatment-emergent. The following defines this group;

- Abnormality satisfies current criteria and occurs first time while the patient is on study treatment (i.e., not seen prior to treatment).
- Abnormality satisfies the current criteria of abnormality, was observed prior to start of treatment, and worsened during study treatment.

The number of patients evaluable for laboratory abnormalities must have at least one observation for at least one test while on treatment. While the number of patients evaluable for clinically significant laboratory abnormalities (includes lab TEAEs) is the number of patients with a clinically significant abnormality for at least one laboratory test while on treatment.

Additional summaries will be produced overall by Maximum CTCAE grade. Frequencies and percentages in each grade and overall will be presented.

Shift in laboratory analyte grade will be characterized by worst on-study CTCAE grade to end of treatment. Shift categories from baseline will be selecting the maximum CTCAE grade for each patient during the study compared to baseline. Grades that are not part of CTCAE grading will be blank. Percentages will be based on the number of patients with non-missing baseline and postbaseline values per each analyte.

9.9.3 Vital Signs

Vital sign parameters: systolic and diastolic blood pressure (mmHg), respiratory rate (breaths per minute), body temperature (C°), weight (kg) and pulse rate (beats per minute)

will be summarized by observed and change from baseline according to minimum and maximum values. Frequency and percentage of patients for each observed parameter outside the normal range during treatment (up to 30 days post last dose date) will be reported. Data will be listed

Table 8 Summary of Vital Signs

Parameter	Units	Normal Range
Systolic Blood Pressure	mmHg	90 - 120
Diastolic Blood Pressure	mmHg	60 - 80
Pulse Rate	Beats per minute	60-100
Respiratory Rate	Breaths per minute	12 – 20

9.9.4 ELECTROCARDIOGRAM (ECG)

The number and percentage of patients with worst ECG result as ordered: abnormal, clinically significant; abnormal, not clinically significant; and Normal. Results will be summarized by treatment at scheduled visits. Results will be counted once for each patient and scheduled visit.

Descriptive summaries of observed and change from baseline values will be presented for ECG measures of HR, PR interval, QRS duration, QT interval, and QTc interval by scheduled visit. QTc interval is derived using Fridericia's correction method. These summaries will be presented by scheduled visit.

For QT interval corrected the following formulas should be used if not entered in the eCRF: Fridericia's correction : QTc = QT/(RR^3)) and Bazett's correction, QTc = QT /SQRT(RR). The number and percentage of subjects having the following notable ECG interval values on treatment will be summarized as follows to evaluate risk of prolongation of QTc interval [as per the definition of International Conference on Harmonization (ICH, 2005)]:

- Maximum QTc intervals > 450 milliseconds, > 480 milliseconds, and > 500 milliseconds.
- Maximum changes from baseline in QTc > 30 and > 60.

ECGs will also be presented in a data listing.

9.9.5 PHYSICAL EXAMS

Physical exam data will be presented in a data listing.

9.9.6 EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

The Eastern Cooperative Oncology Group (ECOG) performance status measures on a scale of 0 (normal activity) to 5 (dead). Frequency and percent for each category per at timepoint will be presented. Data will be presented in subject listings.

9.10 Pharmacokinetic and Immunogenicity Analyses

9.10.1 Pharmacokinetic Analyses

The PK analyses will be based on the PK analysis set, unless otherwise specified.

Plasma concentration data for JTX-2011 will be listed by subject and summarized in tables with standard descriptive statistics by analyte (Drug, i.e., JTX-2011, nivolumab, ipilimumab or pembrolizumab), Part, Dose Level, Cycle, and Time Point. Linear and log-linear plots of concentration versus time will be provided for individual subjects and for means by Drug, Part, Treatment (monotherapy or combination with nivolumab, ipilimumab, pembrolizumab), Dose Level, and Cycle.

PK parameters will be determined by NCA using a validated software platform (WinNonlin/Phoenix™ version 8.0 or higher). Actual sampling times will be used and the estimation method will be linear up, linear down. The analysis will be conducted by or under the oversight of the Clinical Pharmacologist at Jounce. Derived PK parameters will be provided to the statistical department at Jounce to be listed by subject and summarized in tables by Drug, Part, Treatment, Dose Level, and Cycle with descriptive statistics (n, mean, standard deviation, median, minimum, maximum and, for C_{max} and AUC parameters, geometric mean (geo mean) and geometric coefficient of variation (GCV%)).

C_{max}, T_{max}, AUC_{last}, C_{max}/D and AUC_{last}/D will be calculated for all subjects with evaluable concentration-time profiles. The terminal elimination rate constant (λ_z) and parameters requiring λ_z for calculation (AUC_{inf}, AUC_{inf}/D, $t_{½}$, CL_z and V_z) will only be reported when at least 3 points on the terminal elimination phase (excluding C_{max}) can be fit via log-linear regression to a line with an adjusted R^2 value of ≥ 0.9.

In cases where AUC_{inf} can be calculated, only values with extrapolated areas $\leq$20% will be included in summary tables and statistics. All AUC_{inf} values will be reported in the listings, but values with extrapolated areas > 20% will be flagged and footnoted as not included in the summary statistics due to the large percentage of extrapolated area.

Additional PK analysis (population PK/PD modeling or exposure response analysis) may also be conducted and will be documented separately if done.

9.10.2 Immunogenicity Analyses

ADA and NAb titers will be listed by subject. Titers will be summarized by Drug, Part, Treatment, Dose Level, Cycle and Timepoint. The within-cohort (ie by Drug, Part,

Treatment and Dose Level) incidence of ADA and NAb will be summarized using ADA Analysis Set.

ADA and NAb incidence will be presented across all time points on study and by each time point as described below:

- Overall incidence: the number and percentage of subjects that are ADA- or NAb-positive subjects at any point in the study. Each positive subject should be counted only once, regardless of the overall number of positive samples.
- Treatment-induced incidence: the number and percentage of the subjects with at least one positive post-treatment sample who were ADA-negative at baseline.
- Treatment-boosted incidence: the number and percentage of the subjects that were ADA-positive at baseline and have at least one post-treatment result with a higher titer than baseline.

9.11 EFFICACY ANALYSES

Efficacy analyses will be performed using the Response Evaluable Set unless specified otherwise. Summary will be provided separately for each Phase 1 part (A, B, E, G) by dose level and for each Phase 2 part (C, D) by tumor type cohort unless specified otherwise. Data will be presented in subject listings.

9.11.1 ANALYSIS OF RECIST V1.1 RESPONSE

The best overall response (BOR) will be summarized by frequency and percent. The objective response rate (ORR) and disease control rate (DCR) estimates along with the corresponding exact 2-sided 95% CI using the Clopper-Pearson exact method will be provided. This will be done for the both the investigator and the central review response data. Subjects not classifiable under the RECIST 1.1 response categories due to insufficient data or early death will be classified as non-evaluable for BOR, but will be counted in the denominator of response rates (ORR, DCR) calculations.

Waterfall plots for best overall response and maximum percent change from baseline in tumor measurements and spider plots displaying the percent change from baseline in tumor measurements by study day will be displayed for evaluable and subset populations. Additional graphs by disease indication will be created as warranted. All RECIST response assessments will be listed by subject, cohort, phase and visit (including unscheduled). BOR, ORR and DCR will also be included.

9.11.2 ANALYSIS OF IRRC RESPONSE

The irBOR and irORR will be summarized as above in 9.11.1 by frequency and percent along with the corresponding exact 2-sided 95% CI using the Clopper-Pearson exact method however this analysis will only include the central review response data.

Waterfall plots for best overall response and maximum percent change from baseline in tumor measurements and spider plots displaying the percent change from baseline in tumor measurements by study day will be displayed for evaluable and subset populations. Additional graphs by disease indication will be created as warranted. All irRC response assessments will be listed by subject, cohort, phase and visit (including unscheduled). The irBOR and irORR will be included.

9.11.3 Analysis of Time-to-Event Endpoints

Estimates of the duration of response (DOR), landmark and overall survival (OS) and landmark and progression free survival (PFS) will be described using the Kaplan-Meier estimates. If there are sufficient number of events, the median, first and third quartiles (time) and corresponding 2-sided 95% confidence interval based on the Brookmeyer-Crowley methods will be presented. Kaplan-Meier methods will be used to estimate the probability and figures will use the KM estimates to identify the number of subjects at risk at each scheduled visit and will display censored times graphically on the curve. Probability of event estimates will be summarized in a table for various intervals e.g., 3, 6, 9 and 12 months. DOR and PFS will be analysed based on both investigator response data and central review response data. If supported by the data, analyses by disease cohort across phases 1 and 2 may be produced. Analyses of PFS and OS will be done using the SAF and analyses of DOR will be done only for responders(with confirmed CR or PR). KM figures will be produced for PFS and for some selected OS by cohort in both the phase I and phase II.

9.11.4 Comparison of Investigator versus Central Review Response Data

Summaries comparing the BOR and PFS as determined by the investigator versus the central review using RECISTv1.1 criteria will be presented.

9.11.5 Subgroup Analyses

Analysis of response and time to event endpoints outlined above in sections 9.11.1 to 9.11.3 may be performed for the following subgroups:

- ICOS IHC high vs ICOS IHC low on archival tumor sample
- ICOS IHC high vs ICOS IHC low on fresh biopsy
- ICOS IHC 0 vs ICOS IHC 1,2,3 on archival tumor samples
- ICOS IHC 0 vs ICOS IHC 1,2,3 on fresh biopsy
- Prior IO therapy yes or no
- Prior PD-1/PD-L1 therapy yes or no

Subgroup analysis tables will be provided separately for JTX-1011 monotherapy (including 0.1 mg/kg, 0.3 mg/kg and total columns for Part A and tumor cohorts, total columns for Part C) and JTX-1011+Nivolumab combination therapy (including 0.1 mg/kg+ Nivolumab, 0.3 mg/kg + Nivolumab and total columns for Part B and tumor cohorts, total columns for Part D). Additional subgroup analysis, if conducted, will be documented in a separate exploratory analysis plan.

9.11.6 ICOS Target Engagement on CD4 T Cells

ICOS target engagement on CD4 T cells will be presented as % target engagement for each subject in listings. TE will also be presented in tabular format by dose level for each Phase 1 part (A, B, E, G) and by tumor type cohort for each Phase 2 part (C, D) using Biomarker Analysis Set for the following:

- Number and percentage of subjects at each available time point with TE $\geq$ 70%
- Number and percentage of subjects with $\geq$ 70% TE at every measured time point after first dose through C2D1
- Number and percentage of subjects with TE $\geq$ 70% after first dose and descriptive summary of duration of TE $\geq$ 70% after first dose, which is defined as the number of days with TE $\geq$ 70% (only for subjects ever having TE $\geq$ 70% post dose)
- Number and percentage of subjects with TE < 30% after first dose and descriptive summary of duration of TE < 30% after first dose, which is defined as the number of days with TE < 30% (only for subjects ever having TE < 30% post dose)
- Number and percentage of subjects at each available timepoint with TE < 30%
- Number and percentage of subjects at each available time point with TE = 0

The relationship of PK endpoints and ICOS target engagement may also be explored separately using pharmacokinetic/pharmacodynamic (PK/PD) modelling techniques. Any PK/PD modelling will be conducted under a separate analysis plan and reported separately.

9.11.7 Other Exploratory Pharmacodynamic Endpoints

JTXP was intended as an exploratory pharmacodynamics endpoint, but poor sample quality resulted in insufficient data for analysis.

9.12 Interim Analyses

This is an open-label study. No formal interim analyses are planned. However, for Part C and Part D, 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 H0: ORR $\leqslant$ 0.08 versus H1: ORR $\geqslant$ 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) 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 9 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%.

Interim N	Interim β spent	Futility Boundary	Interim result	Expand?	Total N	Final Result
20	0.1%	0	0 OR	Stop for futility	20	Non-significant
			≥1 ORs	Expand	76	If>10 ORs, p-value <5%
15	0	0	0 OR	Stop for futility	15	Non-significant
			≥1 ORs	Expand	76	If>10 ORs, p-value <5%

If the number of responses in any cohort of Parts C or D at interim look is more than the prespecified futility boundary based on the group sequential design, the study may enroll additional subjects for a more robust determination of efficacy.

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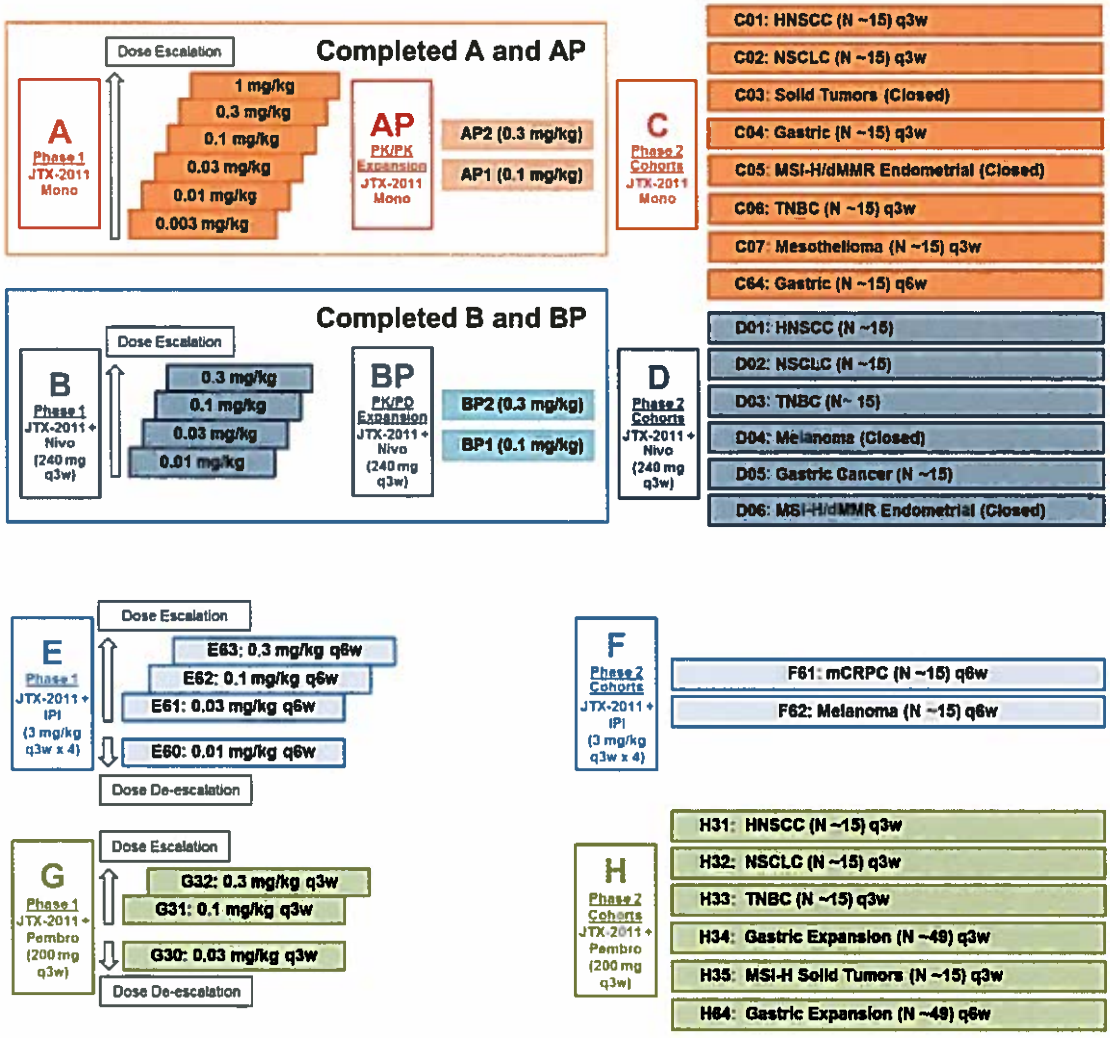
11. APPENDICES

11.1 STUDY DESIGN

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.

11.2 CATEGORIZING LESIONS AT BASELINE

Measurable Lesions - Defined as lesions accurately measured in at least one dimension.

- Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm)
- Lesions with longest diameter at least 20 mm when assessed by Chest X-ray
- Superficial lesions with longest diameter 10 mm or greater when assessed by caliper
- Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

NOTE: Shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

Non-measurable disease - Defined as lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

- Bone disease: Not measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.
- Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is non-measurable unless it has progressed since completion of treatment.

Normal sites

- Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.

- Normal nodes: Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

11.3 RECORDING TUMOR ASSESSMENTS

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 28 days prior to treatment and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be not evaluable.

Target lesions

- All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed on study.
- If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.
- Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded.

NOTE: When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

Non-target disease

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, UNEVALUATED, PRESENT, UNEQUIVOCAL PROGRESSION. Multiple non-target lesions in one organ may be recorded as a single item on the case report form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

11.4 OBJECTIVE RESPONSE STATUS AT EACH EVALUATION

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case must be discussed with the radiologist to determine if substitution is possible. If not, subsequent objective statuses are not evaluable.

Target disease

- Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis < 10 mm). All target lesions must be assessed.
- Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.
- Stable: Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.
- Documented Progression Disease (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.
- Not Evaluable: Progression has not been documented, and
  - one or more measurable target lesions have not been assessed
  - or assessment methods used were inconsistent with those used at baseline
  - or one or more target lesions cannot be measured accurately (e.g., poorly visible unless due to being too small to measure)
  - or one or more target lesions were excised or irradiated and have not reappeared or increased

Non-target disease

- CR: Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be 'normal' in size (<10 mm short axis).
- Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level above the normal limits.
- PD: Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.

- Not Evaluable: Progression has not been determined and one or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.

New Lesions

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

Supplemental Investigations

If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.

If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Symptomatic/clinical progression

Subjects requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumor assessment CRFs. Every effort should be made to document objective progression even after discontinuation of treatment.

Table 1. Objective Response Status at each Evaluation

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR or NA	No	CR
CR	Non-CR/Non-PD or	No (or NE)	PR
PR	CR or Non-	No (or NE)	PR
SD	CR or Non-	No (or NE)	SD
PD	Any	Any	PD
Any	PD	Any	PD
Any	Any	Yes	PD
NE	CR or Non-	No	NE

NA	CR	No	CR
NA	Non-CR/Non-PD	No	SD
NA	NE or NA	No (or NE)	NE
NA	CR or Non-	NE	SD