STATISTICAL ANALYSIS PLAN

Study Title:	Phase 1/1b Study of the Safety of TTX-030 as a Single Agent and in Combination with Pembrolizumab or Chemotherapy in Patients with Lymphoma or Solid Tumor Malignancie
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Analysis Plan Author:	Wei Deng, PhD

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Approved by:

Wei Deng, PhD	Date
Siddhartha Mitra, MD PhD	Date
	Date
	Date

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	adverse events
ALT	alanine transaminase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma/serum concentration versus time curve
BUN	blood urea nitrogen
CIOMS	Council for International Organization of Medical Sciences
CI	confidence intervals
C_{max}	maximum observed plasma/serum concentration of drug
C_{min}	minimum observed plasma/serum concentration of drug
CNS	central nervous system
CRM	Continual reassessment method
CTCAE	common terminology criteria for adverse events
ctDNA	circulating tumor DNA
DDI	drug-drug interaction
DLT	dose limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report forms
EGFR	epidermal growth factor receptor
EOS	end of study
EOT	end of treatment
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Hb	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard Ratio
ICH	International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
ICF	Informed Consent Form
IMP	Investigational Medicinal Product

Abbreviation or Specialist Term	Explanation
IRB	Institutional Review Board
IRR	infusion related reaction
ISH	in situ hybridization
IV	intravenous
IVRS/IWRS	Interactive Voice/Web Response System
KM	Kaplan Meier
LFTs	liver function tests
LVEF	left ventricular ejection fraction
MBC	metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
MAPK	mitogen-activated protein kinase
MRI	magnetic resonance imaging
ms	millisecond
MTD	maximum tolerated dose
MUGA	multigated acquisition
ORR	objective response rate
OS	overall survival
PD	pharmacodynamics
PFS	progression free survival
PI	Principal Investigator
PK	pharmacokinetic
PT	protime
PTT	prolonged protime
QD	once daily
QT	time between the onset of QRS to the end of T wave
QTc	QT interval corrected for heart rate
QTcF	QT interval by Fridericia correction
SAE	serious adverse event
SEM	standard errors of the mean
SOA	schedule of assessments
SOC	standard of care
SOP	Standard Operating Procedures
StD	standard deviation
SUSAR	suspected unexpected serious adverse reactions
$T_{1/2}$	terminal elimination half-life
TEAE	treatment-emergent adverse events
T_{max}	time to reach the highest plasma/serum concentration (observed time point of C_{max})

Abbreviation or Specialist Term	Explanation
ULN	upper limits of normal
Vss	volume of distribution at steady-state
w/v	weight/volume
WBC	white blood cell
WOCBP	woman of childbearing potential

1. BACKGROUND AND RATIONALE

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures and listings (TFLs) of the final analysis in the clinical study report (CSR) for study TTX-030-002. This SAP is based on the study protocol Amendment xx dated xxx.

1.1. Study Design

This is a Phase 1/1b, open-label, multicenter study with a safety lead-in and expansion phase to evaluate the safety/tolerability, preliminary clinical activity, PK, ADA, and pharmacodynamics of TTX-030 in combination with pembrolizumab or budigalimab and/or other chemotherapy in subjects with advanced solid tumors.

Safety Lead-in

The Safety Lead-in Phase includes 2 cohorts as described below and will identify the doses of TTX-030 and budigalimab in combination with chemotherapy or other therapy to be evaluated in the Expansion Phase. The Cohort Review Committee will monitor each cohort during the DLT evaluation period (28-day for TTX-030 regimens given every 2 weeks [Q2W] or 21-day for TTX-030 regimens given every 3 weeks [Q3W] plus a loading dose 7 days prior to Cycle 1 Day 1) and continually evaluate toxicities past the DLT evaluation period.

The Safety Lead-in Cohort 1, conducted in various advanced solid tumors, will identify the doses of TTX-030, budigalimab, and mFOLFOX6 to be evaluated in the Expansion Phase.

In the Safety Lead-in Cohort 1, 6 subjects with various advanced solid tumors will receive the following combination regimen:

- TTX-030 (40 mg/kg 7 days prior to Cycle 1 Day 1 followed by 20 mg/kg Q2W)
- Budigalimab (500 mg every 4 weeks [Q4W])
- mFOLFOX6 (oxaliplatin 85 mg/m^2 IV with leucovorin 400 mg/m^2 IV over 2 hours plus 5-FU 400 mg/m^2 IV bolus and 2400 mg/m^2 continuous infusion over 46 hours Q2W)

In the Safety Lead-in Cohort 2, 6 subjects with mCRPC will receive the following combination regimen:

- TTX-030 (40 mg/kg 7 days prior to Cycle 1 Day 1 followed by 30 mg/kg Q3W)
- Budigalimab (375 mg Q3W)
- Docetaxel (75 mg/m^2 Q3W)

If ≥2 of the 6 evaluable subjects in Safety Lead-in Cohort 2 experience a DLT, either De-escalation Cohort 2a or 2b could be explored based on the toxicity.

In Cohort 2a, 6 subjects will receive the following combination regimen:

- TTX-030 (40 mg/kg 7 days prior to Cycle 1 Day 1 followed by 30 mg/kg Q3W)
- Budigalimab (375 mg Q3W)

- Docetaxel (60 mg/m^2 Q3W)

Expansion Phase

The Expansion Phase includes 6 cohorts, as described below. Multiple expansion cohorts may enroll in parallel. The Sponsor may choose not to open 1 or more of the Expansion cohorts. Expansion of up to 40 subjects in select cohorts will be allowed based on review of safety, efficacy, and statistical considerations by the Sponsor and Cohort Review Committee. Cohorts 5, 6, and 7 were removed/discontinued under Amendment 3, Version 4 of the protocol. Subjects who were screened or enrolled into any of the discontinued cohorts prior to cohort termination will continue on study as per protocol. Expansion Cohorts 5 and 7 were removed under the protocol amendment 3, Version 4.0.

In Expansion Cohorts 3 and 12, a total of approximately 70 response-evaluable subjects (approximately 46 and 24 subjects, respectively) with HER2-negative metastatic GEC will be enrolled (see Inclusion Criteria 16-18 and Exclusion Criteria 20-24). Study treatment will be administered at the doses and schedules identified in the Safety Lead-in Cohort 1.

- Cohort 3 Arm A: TTX-030 + mFOLFOX6 (n=6) [Note: Cohort enrollment discontinued in Amendment 4, Version 5.0]
- Cohort 3 Arm B: TTX-030 + budigalimab + mFOLFOX6 (n=40)
- Cohort 12: Budigalimab + mFOLFOX6 (n=24)

In Expansion Cohorts 4, 6, 8, and 10, up to 23 response-evaluable subjects per cohort with selected advanced solid tumor types (listed below) will receive TTX-030 at the dose identified in the Safety Lead-in combination treatment that includes budigalimab Q3W in a 21-day cycle.

- Expansion Cohort 4: Metastatic CRC that is known to be microsatellite stable and has previously been treated with up to 3 prior systemic chemotherapy regimens for metastatic disease.
- Expansion Cohort 5: [Cohort removed under Amendment 3, Version 4.0].
- Expansion Cohort 6: Recurrent/metastatic HNSCC after progression on immune checkpoint inhibitors (anti-PD-[L]1) primary or secondary resistant. Subjects may have received up to 3 lines of prior systemic therapies for recurrent/metastatic disease. [Cohort enrollment discontinued under Amendment 3, Version 4.0].
- Expansion Cohort 7: [Cohort enrollment discontinued under Amendment 3, Version 4.0].
- Expansion Cohort 8: Advanced unresectable or metastatic adenocarcinoma of the stomach or gastroesophageal junction, previously treated with up to 3 prior systemic therapy regimens for metastatic disease, and anti-PD-L1 naive.
- Expansion Cohort 10: Unresectable or metastatic urothelial cell carcinoma ineligible a) any platinum-containing chemotherapy regardless of PD-L1 status **OR** b) received prior (neo-)adjuvant platinum-containing with disease recurrence >12 months since completion of therapy.

In Expansion Cohorts 9 and 11, approximately 23 response-evaluable subjects per cohort with unresectable or metastatic pancreatic adenocarcinoma (See Inclusion Criteria 32-34) will receive TTX-030 in combination with gemcitabine/nap-paclitaxel ± budigalimab at the RP2D dose(s) for these combinations. If both cohorts are open for enrollment at the same time, cohort assignments will be alternating, or the sponsor will assign the subject to a cohort.

- Expansion Cohort 9: TTX-030 + budigalimab + gemcitabine/nab-paclitaxel (n≤23)
- Expansion Cohort 11: TTX-030 + gemcitabine/nab-paclitaxel (n≤23)

Table 2: Treatment Arm Description

Study Treatment(s)	Cycle	Cohort	Tumor Type	Number of Subjects
TTX-030 (Load+Q2W) + Budigalimab (Q4W) + mFOLFOX6 (Q2W)	28-day	1	Solid tumor malignancy	8
		3 (Arm B)	1L HER-negative GEC	44
Budigalimab (Q4W) + mFOLFOX6 (Q2W)	28-day	12	1L HER-negative GEC (doublet)	25
TTX-030 (Load+Q2W) + mFOLFOX6 (Q2W)	28-day	3 (Arm A)	1L HER-negative GEC	6
TTX-030 (Load+Q3W) + Budigalimab (Q3W) + Docetaxel (Q3W)	21-day	2	Metastatic castration-resistant prostate cancer (mCRPC)	7
TTX-030 (Load+Q2W) + Budigalimab (Q4W) + Gemcitabine + Nab-paclitaxel (Days 1, 8, 15)	28-day	9	Unresectable or metastatic previously untreated pancreatic adenocarcinoma	28
TTX-030 (Load+Q2W) + Gemcitabine + Nab-paclitaxel (Days 1, 8, 15)	28-day	11	Unresectable or metastatic previously untreated pancreatic adenocarcinoma	17
TTX-030 (Load+Q3W) + Budigalimab (Q3W)	21-day	4	Metastatic colorectal cancer (CRC)	14
		6	Recurrent/metastatic head and neck squamous cell carcinoma (HNSCC)	5
		8	Advanced HER2-negative GEC	23
TTX-030 (Load+Q3W) + Pembrolizumab (Q3W)	21-day	10	Unresectable or metastatic urothelial cell carcinoma (UCC)	8

Q2W=every 2 weeks; Q3W=every 3 weeks; Q4W=every 4 weeks.

1.2. Study Objectives and Endpoints

Primary Objectives and Endpoints		
Type	**Objectives**	**Endpoints**
Safety	• Safety Lead-in Cohorts: To assess the safety and tolerability of TTX-030 and budigalimab combination therapy in subjects with various advanced solid tumors • Expansion Cohorts: To assess the safety and tolerability of TTX-030 in combination with pembrolizumab or budigalimab and/or chemotherapy in subjects with selected advanced solid tumors	• Safety Lead-in Cohorts: The incidence of AEs and DLTs, as well as changes from baseline in vital signs, clinical laboratory parameters, physical examination findings, ECOG performance status, and ECG results • Expansion Cohorts: The incidence of AEs, as well as changes from baseline in vital signs, clinical laboratory parameters, physical examination findings, ECOG performance status, and ECG results
Secondary Objectives and Endpoints		
Type	**Objectives**	**Endpoints**
Efficacy	• Safety Lead-in Cohorts: To determine the preliminary clinical activity of TTX-030 and budigalimab combination therapy in subjects with various advanced solid tumors • Expansion Cohorts: To determine the clinical activity of TTX-030 in combination with pembrolizumab or budigalimab and/or chemotherapy therapy in subjects with selected advanced solid tumors	• ORR, BOR, DoR, DCR (defined as CR, PR, or SD), PFS per RECIST v1.1 and iRECIST, and OS. For prostate adenocarcinoma, PCWG3 will be used.
PK	• Safety Lead-in Cohorts: To describe the PK profiles of TTX-030 in subjects with various advanced solid tumors • Expansion Cohorts: To describe the PK profiles of TTX-030 in subjects with selected advanced solid tumors	• Serum concentration and PK parameters for TTX-030
ADA	• Safety Lead-in Cohorts: To describe the immunogenicity of TTX-030 in subjects with various advanced solid tumors • Expansion Cohorts: To describe the immunogenicity of TTX-030 in subjects with selected advanced solid tumors	• Number and percentage of subjects who develop ADA to TTX-030
Exploratory Objective and Endpoint		
Type	**Objective**	**Endpoint**
Pharmaco-dynamics	• To assess the effects of TTX-030 and budigalimab on pharmacodynamic biomarkers in peripheral blood and tumor tissue relating to mechanism of action, immune responses, and associated with PK/safety	Pharmacodynamic biomarkers and correlatives: • Exploratory pharmacodynamic biomarkers

ADA=antidrug antibody; AE=adverse event; BOR=best overall response; CR=complete response; DCR=disease control rate; DLT=dose-limiting toxicity; DoR=duration of response; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; iRECIST=immunotherapy Response Evaluation Criteria for Solid Tumors; ORR=objective response rate; OS=overall survival; PCWG3=Prostate Cancer Working Group 3; PFS=progression-free survival; PK=pharmacokinetics; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease

1.3. Sample Size

Safety Lead-in

The planned sample size for the Safety Lead-in is a minimum of 6 subjects for each cohort. More subjects may be enrolled if lower doses are explored. Subjects are considered DLT evaluable if they complete the DLT evaluation period or experience a DLT during the DLT evaluation period (28-day for TTX-030 regimens given every 2 weeks [Q2W] or 21-day for TTX-030 regimens given every 3 weeks [Q3W] plus a loading dose 7 days prior to Cycle 1 Day 1). A subject not evaluable for DLT will be replaced with another subject at the same dose level.

Expansion Phase

The planned sample size is approximately 70 response-evaluable subjects for Expansion Cohorts 3 and 12 (approximately 46 and 24 subjects, respectively) and up to 115 subjects for Expansion Cohorts 4, 8 through 11 (up to 23 response-evaluable subjects per cohort [Cohorts 5 and 7 were removed under Amendment 3, Version 4.0 and enrollment into Cohort 6 was discontinued]). The sample size was selected to evaluate the safety profile and preliminarily efficacy. An informal interim analysis may be performed when 14 subjects have been treated in an expansion cohort. Enrollment may continue during the analysis. A second expansion of up to 40 response-evaluable subjects in select cohorts will be allowed based on review of safety, efficacy, and statistical considerations by the Sponsor and Cohort Review Committee. A subject who does not reach a first post-baseline scan (non-evaluable) will be replaced with another subject at the same dose level.

With a maximum sample size of 46, 24, or 23 response-evaluable subjects, the probability to observe at least 1 occurrence of AE is ≥99.2%, ≥92.0%, or ≥91.1%, respectively, if the true incidence of the respective AE rate is ≥10%, respectively.

The goal of the sample size determination is a lower bound of the CI that will exclude 30% (or lower) response rates for Expansion Cohorts 3 and 12 and 5% (or lower) response rates for Expansion Cohorts 4, 8-11, as measured by ORR. Table 3 provides the exact 80% CI corresponding to various observed response rates assuming a total of 46, 24, or 23 response -evaluable subjects in each cohort.

Table 3: Exact 1-Sided 80% CIs from Various Response Rates

Cohort size (n)	Number of Responders	Observed Response Rate	Exact 80% CI
40 (Arm B in Cohort 3)	15	38%	(0.302, 1)
	16	40%	(0.326, 1)
	18	45%	(0.373, 1)
	20	50%	(0.422, 1)
	25	63%	(0.546, 1)
24 (Cohort 12)	10	42%	(0.317, 1)
	11	46%	(0.356, 1)
	12	50%	(0.396, 1)
	14	58%	(0.477, 1)
	16	67%	(0.560, 1)
23 (Cohorts 4, 8-11)	3	13%	(0.068, 1)
	4	17%	(0.102, 1)
	5	22%	(0.137, 1)
	7	30%	(0.212, 1)
	9	39%	(0.291, 1)
	11	48%	(0.372, 1)

CI=confidence interval.

2. TYPE OF PLANNED ANALYSES

The final analysis of the data will be performed when all patients completed the End of Study (EOS) visit, after outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

3. GENERAL CONSIDERATIONS

All statistical tabulations and analyses will be done using SAS®, Version 9.4 or higher.

Unless otherwise noted, continuous variables will be summarized using the number of subjects (n), mean, standard deviation (StD), median, minimum, and maximum; categorical variables will be summarized using the number and percentage of subjects in each category.

By-subject listings will be presented for all subjects in the Full Analysis Set and sorted by phase, treatment group, subject ID number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within the subject. The treatment group to which subjects were enrolled will be used in the listings. Age, sex at birth, race, and ethnicity will be included in the listings, as space permits.

The summaries of efficacy data will be presented by treatment group.

3.1. Analysis Sets

3.1.1. Full Analysis Set

The Full Analysis Set (FAS) consists of all subjects who are enrolled in the study. The Full Analysis Set will be used for subject disposition, baseline characteristics, and efficacy endpoints.

3.1.2. Safety Analysis Set

The Safety Analysis Set consists of all subjects who have received at least 1 dose or any partial dose of study treatment.

The Safety Analysis Set will be used for safety endpoints and study treatment administration.

3.1.3. Efficacy-Evaluable Analysis Set

The Efficacy-Evaluable Analysis Set includes all subjects in the Safety Analysis Set, had at least 1 postbaseline evaluable tumor assessment unless death or clinical progressive disease occurred prior to the first post baseline disease assessment.

The Efficacy-Evaluable Analysis Set will be used in the primary analyses of efficacy endpoints.

3.1.4. DLT-Evaluable Analysis Set

The DLT-Evaluable Analysis Set consists of all subjects in the dose escalation cohorts who received one infusion during the treatment cycle and completed safety evaluations through the end of the DLT period or experienced a DLT prior to the end of the DLT period (i.e. start Cycle 2 or experienced a DLT).

DLTs will be evaluated in the DLT-Evaluable Analysis Set.

3.1.5. PK Analysis Set

The PK Analysis Set consists of all subjects in the Safety Analysis Set who have the necessary baseline and on-study PK measurements to provide interpretable results for the PK parameters. Subject may be removed from the estimation of certain PK parameters depending on the number of available blood samples. These subjects will be identified at the time of analysis.

The PK Analysis Set is the primary analysis set for all PK analyses.

3.2. Subject Grouping

Subjects will be grouped according to the actual treatment they received. Subjects in the dose expansion (randomized in Arm 1 and 2; non randomized in Arm 3) as well as in the safety lead-in will be pooled for summary.

Summaries will be provided separately for the following groups of subjects:

- Chemotherapy Combinations: Cohorts 1, 2, 3 (Arm A), 3 (Arm B), 11 and 12
- PD-1 Combinations: TTX-030 + budigalimab (Cohorts 4, 6 and 8); TTX-030 + pembrolizumab (Cohort 10)

3.3. Examination of Subject Subgroups

The following subgroups may be examined for efficacy and safety analyses.

- Age (<65; ≥65 yrs)
- Gender (male; female)
- Race (white; black of African American; Asian; other)
- Measurable disease (Yes; No)
- Cancer type (RCC, pancreatic cancer, other)

3.4. Multiple Comparisons

Adjustments for multiplicity will not be made, because no formal statistical testing will be performed in this study.

3.5. Missing Data and Outliers

3.5.1. Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified.

The handling of missing or incomplete dates for disease diagnosis and prior anticancer therapy is described in Section 5.3; for prior and concomitant medications in described in Section 5.4; for new anticancer therapy is described in Section 6.1, for AE onset is described in Section 7.1.5.

3.5.2. Outliers

Outliers will be identified during the data management and data analysis process, but no sensitivity analyses will be conducted. All data will be included in the data analysis.

3.6. Data Handling Conventions and Transformations

All serum concentrations reported as No Result (NR or Not Collected/Not Done, ND) values will be treated as missing and will appear in the data set as ".". For the purpose of calculating or plotting mean concentration-time data, or calculating PK parameters, concentration values determined to be below the limit of quantitation (BLQ) will be treated as zero if they occur prior to the first measurable concentration; all other BLQ values will be treated as missing and set to ".". Quantifiable concentrations after two consecutive BLQ values following the same dose will also be set to "." for the purposes of calculating PK parameters.

3.7. Analysis Visit Windows

3.7.1. Definition of Study Day

Study day will be calculated from the first dosing date of any portion of the study drug:

- Postdose Study Days = Assessment Date – First Dosing Date + 1
- Study Day prior to First Dose = Assessment Date – First Dosing Date

3.7.2. Analysis Visit Windows

No analysis visit window will be assigned in the analysis as no summary by visit is planned.

3.7.3. Selection of Data

In general, the baseline value will be the last non-missing value on or prior to the first dosing date of study drug unless specified differently.

For continuous measurements, if multiple measurements occur on the same day, the last non-missing value will be considered as the baseline value. If these multiple measurements occur at the same time or the time is not available, the average of these measurements will be considered the baseline value. For categorical measurements, if multiple measurements occur on the same day, the last non-missing value will be considered as the baseline value. If these multiple measurements occur at the same time or the time is not available, the value with the lowest severity will be considered the baseline value.

Measurements occurred after first dose date will be considered postbaseline values.

4. STUDY DISPOSITION

4.1. Subject Enrollment and Disposition

A summary of subject disposition will be provided by treatment group. Percentages will be based on the Safety Analysis Set. The number of subjects in the following categories will be provided:

- Signed the inform consent
- Received any study treatment
- Continuing study treatment
- Discontinued from study treatment with reasons for treatment discontinuation
- Continuing study
- Discontinued from study with reasons for study discontinuation

4.2. Extent of Exposure and Adherence

Descriptive statistics of extent of exposure will be presented by treatment group for each component of study treatment (TTX-030, budigalimab , mFOLFOX6, docetaxel, nab-paclitaxel, gemcitabine and pembrolizumab):

- Duration of exposure (weeks)
- Cumulative exposure by week
- Total number of infusions
- Dose intensity

Total duration of exposure to study drug (in weeks) will be defined as following, regardless of any temporary interruptions in study drug administration.

- TTX-030, budigalimab and Pembrolizumab: (last available dosing date – first dosing date + 21) / 7
- Gemcitabine: (last available dosing date – first dosing date + 7) / 7
- Nab-paclitaxel, docetaxel and mFOLFOX6: (last available dosing date – first dosing date + 14) / 7

Dose intensity is defined as 100*(Total study drug administered in mg / Total study drug expected to be administered in mg during exposure to study drug). Percentage of subjects in the intensity categories (<75% and ≥75%) will be provided.

The number and percentage of subjects who have dose reduction, dose delay or interruption will be summarized with reasons.

Summaries of exposure will be performed with the Safety Analysis Set. A by-subject listing of study drug administration will be provided.

5. DEMOGRAPHICS AND BASELINE

5.1. Demographics

Demographic data will be summarized using descriptive summary statistics for the Safety Analysis Set. The demographic characteristics include age, sex, race and ethnicity.

On the CRF for demographics, as long as 'Decline to Specify' is checked for race, race will be summarized under the category 'Decline to Specify' even if other categories are also checked.

A by-subject listing will be provided for demographic data.

5.2. Other Baseline Disease Characteristics

Other baseline characteristics include body height (in cm), body weight (in kg), body mass index (BMI; in kg/m^2), body surface area (BSA; in m^2), and baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS).

5.3. Medical History

Medical history will be collected at screening for disease-specific and general conditions (ie, conditions not specific to the disease being studied).

A summary of disease-specific medical history will be provided for the Safety Analysis Set as part of the disease-specific baseline characteristics. Time since initial diagnosis of cancer (months) and time since diagnosis of unresectable disease (months) will be calculated by (date of first dose – date of initial diagnosis) / 30.4375. They will be summarized using summary statistics for a continuous variable. Disease stage at diagnosis and at screening will be summarized using summary statistics for a categorical variable.

In deriving the time since diagnosis, all partial dates of diagnosis and last regimen will be identified, and the partial dates will be imputed as follows:

- If day and month are missing but year is available, then the imputed day and month will be 01 Jan.
- If day is missing but the month and year are available, then the imputed day will be the first day of the month.
- Partial date will not be imputed if the year is missing.

General medical history data will be listed only. By-subject listings will be provided for disease-specific medical history and general medical history.

5.4. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary –WHODD and classified according to ATC codes levels 2 (therapeutic sublevel) and 4 (chemical sublevel).

All medications with an end date prior to the first dose of any study drug will be considered as prior medication regardless of the stop date. If a partial start date is entered the medication will be considered prior unless the month and year (if day is missing) or year (if day and month are missing) of the start date are after the first dosing date. Medications with a completely missing start date will be considered as prior medication, unless otherwise specified.

Concomitant medications are defined as medications taken while a subject took study drug. If a partial stop date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration will not be considered as concomitant medication. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the study drug stop date will not be considered as concomitant medication. Medications with completely missing start and stop dates will be considered as concomitant medication, unless otherwise specified.

All prior and concomitant medications (other than per-protocol study drugs) will be provided in a by-subject listing.

5.4.1. Prior Anticancer Therapy

Number of prior regimens, time since the completion of last regimen will be summarized by treatment group using descriptive statistics. The best response to the last regimen will be summarized using summary statistics for a categorical variable. The summaries will be based on the Full Analysis Set as part of the disease-specific baseline characteristics. A partial completion date will be imputed using the algorithm defined in Section **Error! Reference source not found.**. The prior anticancer therapy will be listed by subject.

6. EFFICACY ANALYSES

Efficacy summaries will be presented by treatment group based on the Efficacy-Evaluable Analysis Set.

6.1. Objective Response Rate (ORR)

The primary efficacy endpoint is objective response rate (ORR) as assessed by the investigators per iRECIST. The ORR is defined as the proportion of subjects who achieved a best overall response (BOR) of complete response (iCR) and partial response (iPR) as defined in iRECIST. Confirmation of iCR/iPR is required for this study.

Per iRECIST, the BOR is defined as the best response in the order of the following, documented from first dose of study treatment until the end of study, first disease progression, death, or start of new anti-cancer therapy, whichever is earlier:

- Complete Response (iCR)
- Partial Response (iPR)
- Stable Disease (iSD)
- Progressive Disease (iPD)
    - Unconfirmed Progressive Disease (iUPD) or
    - Confirmed Progressive Disease (iCPD)

The ORR defined per RECIST v1.1 will also be analyzed in this study. The details for ORR per RECIST v1.1 are provided in greater details below. Even though ORR per iRECIST was the primary efficacy endpoint defined in the protocol, ORR per RECIST v1.1 will be the primary focus evaluating the treatment efficacy of this study. ORR per iRECIST will be analyzed similarly as ORR per RECIST v1.1, with an 1-on-1 match of BOR (iCR to CR; iPR to PR; iSD to SD; and iPD to PD).

The ORR per RECIST v1.1 is defined as the proportion of subjects who achieve best overall response (BOR) of either complete response (CR) or partial response (PR) as derived based on the lesion measurement provided by the investigators per RECIST v1.1. The BOR is the best response (in the order of CR, PR, stable disease [SD], and progressive disease [PD]) documented from first dose until the end of study, first disease progression, death, or start of new anti-cancer therapy, whichever is earlier. A BOR of SD can only be made after the subject is on-study for a minimum of 6 weeks (42 days) ± 7 days. If the subject is on-study less than 5 weeks (35 days), any tumor assessment indicating SD before this time period will have a BOR of not evaluable (NE) unless PD is identified. Subjects, who do not have sufficient baseline or on-study tumor status information to be adequately assessed for response status (ie, those with BOR of NE), or

have received anticancer therapy other than the study treatment prior to achieving CR or PR, will be considered as non-responders and will be included in the denominators in calculations of response rates.

Timepoint tumor responses will be derived based on the target lesion, non-target lesion and new lesion assessments provided by the investigators as per RECIST v1.1.

Confirmation of CR/PR is required for this study. Determination of BOR with confirmation of CR/PR is shown in Table 4. A Best Response of CR/PR cannot be assessed unless it is confirmed, no earlier than 4 weeks (28 days) from the time a response or CR/PR is first suspected (SD does not require confirmation). Subsequent documentation of a CR may provide confirmation of a previously identified CR even with an intervening NE (e.g., CR NE CR). Subsequent documentation of a PR may provide confirmation of a previously identified PR even with an intervening NE or SD (e.g. PR NE PR or PR SD PR). However, only one intervening NE or SD will be allowed between PRs for confirmation.

Table 4: Confirmed Response based on Subsequent Assessment*

First Time Point Response**	Second Time Point Response	Confirmed Response (Best Response)*
PD	No further evaluation	PD
NE	PD	PD
CR	PD	SD or PD (1)
PR	PD	SD or PD (1)
SD	PD	SD or PD (1)
CR	CR	CR
CR	NE**	SD or NE (2)
PR	CR	PR
PR	PR	PR
PR	SD (3)**	SD
PR	NE**	SD or NE (2)
SD	CR	SD
SD	PR	SD
SD	SD	SD
SD	NE	SD or NE (2)
NE	CR	SD
NE	PR	SD
NE	SD	SD
NE	NE	NE

* A Best Response of SD can only be made after the subject is on-study for a minimum of 6 weeks (42 days) ± 7 days. If the subject is on-study less than 5 weeks (35 days), any tumor assessment indicating stable disease (SD) before this time period will have a BOR of NE unless PD is identified.

** Subsequent documentation of CR may provide confirmation of a previously identified CR for subjects where the second integrated response was NE. Subsequent documentation of PR may provide confirmation of a previously identified PR for subjects where the second integrated response was NE or SD. If the third time point response (TPR) confirms the CR (or PR) then the Confirmed Response will be CR (or PR). For this study, only one intervening NE is allowed between CRs/PRs. For example: CR NE CR = CR; PR NE PR = PR. Additionally, one SD is allowed between PRs (e.g., PR SD PR = PR).
(1) Best Response will be SD if the first TPR is after 5 weeks (35 days) on-study. Otherwise, the best response will be PD.
(2) Best Response will be SD if the first TPR is after 5 weeks (35 days) on-study. Otherwise, the best response will be NE.
(3) TPR is SD if the increase from the first to the second assessment does not qualify for PD.

When the date of initiation of new anticancer therapy other than the study treatment is incomplete or missing, the following algorithm will be followed:

- If the day is missing but the month and year are available, then the imputed day will be the last day of the month.
- If day and month are missing but year is available, then the imputed day and month will be the last day of the month for the last adequate disease assessment if they have the same year.

The following will be performed based on Efficacy-Evaluable Analysis Set:

- Best overall response will be summarized using the number and the percentage of subjects in each category (confirmed CR, confirmed PR, SD, PD or NE)
- Reasons for subjects being not evaluable for assessment will also be provided
- Confirmed ORR will be presented with corresponding 2-sided 95% CI based on Clopper-Pearson method. Non-responders will be included in the denominator only.

By-subject listings will be provided for target lesion, nontarget lesion, new lesion, and investigator-assessed timepoint response. A by-subject listing of new anticancer therapy will also be provided.

6.2. Duration of Response (DoR)

Duration of response (DoR) per RECIST v1.1 is defined as the time interval between the date of the first documentation of objective response (CR or PR) and the date of the first objective documentation of disease progression or death due to any cause.

DoR (months) = (date of event or censoring – date of first CR or PR + 1)/30.4375

DoR will be evaluated on subjects who achieve a confirmed CR or PR.

DoR per iRECIST will be analyzed similarly.

6.3. Disease Control Rate (DCR)

Disease control rate (DCR) per RECIST v1.1 is defined as the proportion of subjects who achieve a CR, PR or SD.

DCR will be presented with corresponding 2-sided 95% exact confidence intervals based on Clopper-Pearson method. Subjects who do not achieve CR, PR or SD will be included in the denominator only.

DCR per iRECIST will be analyzed similarly.

6.4. Progressive-Free Survival (PFS)

Progression-free survival (PFS) is defined as the time interval from the first dose of study treatment to the earlier of the first documentation of definitive disease progression or death from any cause. Definitive disease progression is determined based on RECIST v1.1.

The date of definitive progression will be the time point at which progression is first identified by relevant radiographic, imaging, or clinical data. Data will be censored on the date of last adequate tumor assessment for subjects:

- who do not have disease progression or die after study discontinuation, or
- who start new anticancer therapy other than the study treatment prior to documented disease progression, or
- who have ≥ 2 consecutive missing tumor assessments before disease progression or death

If a subject does not have a baseline tumor assessment, then the PFS time will be censored at Study Day 1, regardless of whether or not definitive disease progression or death has been observed.

PFS analysis will be conducted for subjects in the Efficacy-Evaluable Analysis Set. Medians, Q1, and Q3 of PFS and the proportion of subjects who are progress-free at 3, 6, 9, and 12 months from Study Day 1 will be derived using Kaplan-Meier (KM) methods. A listing will be provided for the information of subject PFS.

PFS per iRECIST will be analyzed similarly.

6.5. Overall Survival (OS)

Overall survival (OS) is defined as the time interval from the first dose of study treatment to death from any cause. Subjects who are lost to follow-up or survived until the end of the study will be censored at the last date that they were known to be alive. OS analysis will be conducted for subjects in the Efficacy-Evaluable Analysis Set. Medians, Q1, and Q3 of OS and the proportion of subjects who are alive at 3, 6, 9, and 12 months from Study Day 1 will be derived using KM methods. A listing will be provided for the information of subject OS.

6.6. Other Efficacy Endpoints

6.6.1. Time to Response (TTR)

Time to response (TTR) is defined as the interval from the first dose of TTX-030 to the first documentation of CR/PR.

TTR (months) = (date of first CR/PR – first dose date + 1) / 30.4375

TTR will be evaluated on subjects who achieve a CR or PR in the Efficacy-Evaluable.

6.6.2. Percent Change in Tumor Size

Tumor size based on the sum of the diameters of target lesions is collected on the eCRF through an MRI/CT scan every 9 weeks postbaseline. Percent change from baseline will be determined for each postbaseline assessment. The best percent change from baseline is defined as the largest percentage decrease in tumor size while the subject was on-treatment prior to the time of initiation of anticancer therapy other than the study treatment. If a subject only experienced tumor size increase, then the best percent change from baseline is the smallest increase.

- The percent (%) change from baseline = (Post-baseline assessment – baseline assessment) / baseline assessment x 100
- The best percent (%) change from baseline = the minimum of % change from baseline

Percent change in tumor size will be analyzed on the Efficacy-Evaluable Analysis Set for subjects with baseline and at least 1 postbaseline assessment. Descriptive statistics will be presented by dose level for the best percent change from baseline in tumor size. Waterfall plot will also be provided by dose level. Listings of target, nontarget and new lesions will also be provided.

6.6.3. ECOG PS

The ECOG performance status score has a range from 0 (Fully active; able to carry on all pre-disease performance without restriction) to 5 (Dead). The baseline ECOG PS is summarized in the disease-specific baseline characteristics as specified in Section **Error! Reference source not found.**. A listing of ECOG performance status will be provided.

6.7. Changes from Protocol-Specified Efficacy Analysis

BOR and TTP are removed as study endpoints.

ORR and PFS per RECIST v1.1 are added.

Definitions for analysis population are updated.

7. SAFETY ANALYSES

Unless otherwise specified, all analyses will be performed using the Safety Analysis Set.

No formal comparisons of safety endpoints are planned.

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

All AEs will be coded to SOC and PT using Medical Dictionary for Regulatory Activities (MedDRA).

7.1.2. Adverse Event Severity

Adverse events are graded for severity by the investigators using the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) Version 5.0. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings.

7.1.3. Relationship of Adverse Event to Study Drug

A treatment related AE is an AE noted as related or possibly related to TTX-030, pembrolizumab, gemcitabine or nab-paclitaxel by the investigator. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-subject data listings will show the relationship as missing.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AEs met the definitions of SAEs that were specified in the study protocol.

7.1.5. Treatment-Emergent Adverse Events (TEAE)

A treatment-emergent AE (TEAE) is defined as an AE that was not present prior to the start date of study drug or was worsened during treatment and 90 days after permanent discontinuation of study drug. An AE that was present at treatment initiation but resolved and then reappeared and the event severity increase while the subject was on treatment is also a TEAE.

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dosing date of study drug, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment emergent. The event is considered treatment emergent if both of the following 2 criteria are met:

- The AE onset is the same as or after the month and year (or year) of the first dosing date of study drug, and
- The AE onset date is the same as or before the month and year (or year) of the date

corresponding to 90 days after the date of the last dose of study drug

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dosing date of study drug, will be considered treatment emergent. In addition, an AE with the onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dosing date of study drug will be considered treatment emergent.

7.1.6. Summary of Adverse Events and Deaths

The number and percentage of subjects who experienced at least 1 TEAE will be provided and summarized by SOC, PT, and treatment group. For other AEs described below, summaries will be provided by SOC, PT, maximum severity, and treatment group

- TEAE
- TE SAE
- Summary of TEAE of Grade 3-5
- TEAE related to TTX-030
- TEAE related to budigalimab
- TEAE related to mFOLFOX6
- TEAE related to docetaxel
- TEAE related to gemcitabine
- TEAE related to nab-paclitaxel
- TEAE related pembrolizumab
- TE SAE related to TTX-030
- TE SAE related to budigalimab
- TE SAE related to mFOLFOX6
- TE SAE related to docetaxel
- TE SAE related to gemcitabine
- TE SAE related to nab-paclitaxel

- TE SAE related to pembrolizumab
- TEAE leading to TTX-030 treatment discontinuation
- TEAE leading to budigalimab treatment discontinuation
- TEAE leading to mFOLFOX6 treatment discontinuation
- TEAE leading to docetaxel treatment discontinuation
- TEAE leading to gemcitabine treatment discontinuation
- TEAE leading to nab-paclitaxel treatment discontinuation
- TEAE leading to pembrolizumab treatment discontinuation
- TEAE leading to death
- TEAE of dose limiting toxicity

A brief, high-level summary of AEs described above will be provided by treatment group and by the number and percentage of subjects who experienced the above AEs.

Multiple events will be counted only once per subject in each summary. AEs will be summarized in alphabetic order of SOC and then by PT in descending order of total frequency within each SOC. For summaries by severity, the most severe severity will be used for those AEs that occurred more than once in a subject.

In addition to the above summary tables, TEAEs will be summarized by PT only in descending order of total frequency.

All AE and recorded deaths for the safety population will be listed.

7.1.7. Dose-Limiting Toxicity

The summary and listing of DLTs will be performed on the DLT-Evaluable Analysis Set. A summary of DLT which occurred in Cycle 1 will be provided by SOC, PT, and severity. All DLTs will be listed.

7.1.8. Adverse Events of Special Interest

AESI for the purposes of this study are tumor lysis syndrome (TLS), cytokine release syndrome (CRS) and immune-related adverse events. In addition, infusion related reactions will be summarized, identified as TEAEs with hypersensitivity (SMQ).

The AESI will be summarized similarly to TEAE by treatment arms. The following summaries may be provided as appropriate for subjects:

- Re-challenged after dose interruption due to AESI
- Re-challenged successfully after interruption with resumption of study drug at a starting dose
- Re-challenged successfully after interruption with resumption of study drug at a reduced dose
- With recurrence of AESIs among re-challenged

Time to first onset of AESI and time to resolution may be summarized and plotted as appropriate. KM estimates of the median, Q1, Q3 and the number of subjects with event and censored subjects will be provided.

Time to onset of first event is defined as time from start of study treatment to the date of first incident AESI. In the absence of an event, the censoring date applied will be the earliest from the following dates: last dosing date of study drug + 90 days or death date. Time to resolution of AESI is calculated as AE resolution date – start date of first occurrence of AE + 1.

For better evaluation of the AESI, patient profile including study drug exposure, AESI, concomitant medication, laboratory abnormalities and other events may be provided.

7.2. Clinical Laboratory

Summaries of laboratory data will be provided in the Safety Analysis Set and will include data collected up to the last dose of study drug plus 90 days for subjects who have discontinued study drug, or all available data at the time of the final analysis data-cut for subjects who are ongoing at the time of the final analysis.

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

Summary of laboratory abnormalities with CTCAE v5.0 will be provided by lab test and treatment group. Subjects will be categorized according to the most severe postbaseline abnormality grade for a given laboratory test.

A by-subject listing of laboratory test results collected throughout the study will be provided

7.3. Body Weight and Vital Signs

Descriptive statistics will be provided by treatment group for body weight and vital signs as follows:

- Baseline
- Postbaseline maximum

- Postbaseline minimum
- Change and percentage change from baseline to postbaseline maximum
- Change and percentage change from baseline to postbaseline minimum

A baseline value is defined as the last available value collected on or prior to the first dose of study drug.

A by-subject listing of body weight and vital signs will be provided by subject ID and time point in chronological order

7.4. Electrocardiograms

Subjects with abnormal ECG findings will be listed only.

7.5. Other Safety Measures

By-subject listings for pregnancy report will be provided.

8. PHARMACOKINETICS (PK) AND PHARMACODYNAMICS (PD)

8.1. Pharmacokinetics (PK)

The analysis plan of pharmacokinetics will be provided in a stand alone document, which is outside the scope of this SAP.

8.2. Pharmacodynamics (PD)

The analysis plan of pharmacodynamics will be provided in a stand alone document, which is outside the scope of this SAP.

9. LIST OF REFERENCES

Eisenhauer EA, Thereasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guidelines (version 1.1). *Eur J Cancer*. 2009. Jan;45(2):228-47.

Liu S. and Yuan, Y. Bayesian optimal interval designs for phase I clinical trials. *Journal of the Royal Statistical Society. Series C: Applied Statistics*. 2015. 64(3), 507-523.

Yuan Y, Hess KR, Hilsenbeck SG, Gilbert MR. Bayesian Optimal Interval Design: A Simple and Well-Performing Design for Phase I Oncology Trials. *Clin Cancer Res*. 2016. 22(17):4291-4301.

Zhou H, Lee JJ, Yuan Y. BOP2: Bayesian optimal design for phase II clinical trials with simple and complex endpoints. *Statistics in Medicine*. 2017. 36(21):3302-3314.

Zhou H, Yuan Y, Nie L. Accuracy, safety, and reliability of novel phase I trial designs. *Clinical Cancer Research*. 2018. 24(18), 4357-4364.

10. SOFTWARE

SAS® Software Version 9.4. SAS Institute Inc., Cary, NC, USA

11. APPENDICES

Appendix 1. Schedule of Assessments

Assessments	Schedule	Screening	Baseline	Loading Dose	C1D1	C1D2	C1D3	C1D8	C1D15	C1D22	C2D1	C2D8	C2D15	C3D1	C3D15	C4D1	CXD1#	EOT
Informed Consent, Entry Criteria, Demographics, Medical History, ECG, HgbA1c	All	x																
Physical Exam	Q2W	x	x	x					x		x		x	x	x	x	x	x
	Q3W																	
Symptom Directed Exam	Q2W				x	x		x		x								
	Q3W								x			x						
Vital Signs	Q2W	x	x	x	x	x		x	x	x	x		x	x	x	x	x	x
	Q3W											x						
ECOG	All	x			x						x			x		x	x	x
Tumor Assessment and serum tumor markers[1]	All	x												x		x	x	
Thyroid Function Test	All		x	x														
Lab - Chemistry & Hematology	Q2W	x	x	x			x	x	x	x	x			x		x	x	x
	Q3W						x											
	Q4W									x								
ACTH, FSH, LH, GH amylase and lipase	All		x															
Lab - Coagulation	Q2W	x	x	x				x	x	x	x			x		x	x	x
	Q3W																	
Lab - Pregnancy	All	x	x	x							x			x		x	x	x
TTX-030 Administration	Q2W			x	x				x		x		x	x	x	x	x	
	Q3W																	
Companion Tx Admin[2]	Q2W				x			x	x		x		x	x	x	x	x	
	Q3W																	
PK Samples	Q2W			x	x	x		x	x	x	x		x	x		x	x	x
	Q3W						x											
ADA Samples	Q2W		x		x	x			x		x			x		x	x	x
	Q3W																	
Pharmacodynamic samples	Q2W		x	x	x	x	x	x	x		x			x		x	x	x
	Q3W																	
Tumor Biopsy	All	x									x							

CxD1#: repeated at xD intervals based on QxW. i.e Q2W and Q4W is every 28 days, and Q3W is every 21 days

[1] Tumor Assessments (both CT/PET-CT and serum) are 7 days (4 days for Q3W for C1D1) prior to the visits and are repeated at 8-week intervals (starting at C4D1) for Q2W and Q4W dosing groups and are repeated at 9-week intervals (starting at C5D1) for Q3W dosing groups.

[2] pembrolizumab or gemcitabine+nab-paclitaxel

Appendix 2. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)

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

Signature: *Electronically signed by: Siddhartha Mitra*
Reason: Approver - Chief Medical Officer
Date: Feb 26, 2024 09:12 PST

Email: smitra@trishulatx.com

Signature: Wei Deng *Electronically signed by: Wei Deng*
Reason: Author
Date: Feb 26, 2024 18:19 PST

Email: wdeng@trishulatx.com