STATISTICAL ANALYSIS PLAN

Study Title:	**An Open-Label Multicenter 3-Arm Randomized Phase 2 Study to Assess the Efficacy and Safety of TTX-030 and Chemotherapy With or Without Budigalimab, Compared to Chemotherapy Alone, for the Treatment of Patients not Previously Treated for Metastatic Pancreatic Adenocarcinoma**
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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
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
IRB	Institutional Review Board

Abbreviation or Specialist Term	Explanation
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
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})
ULN	upper limits of normal
Vss	volume of distribution at steady-state

Abbreviation or Specialist Term	Explanation
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 analyses (both the interim futility analyses and the final analysis) in the clinical study report (CSR) for study TTX-030-003.

1.1. Study Design

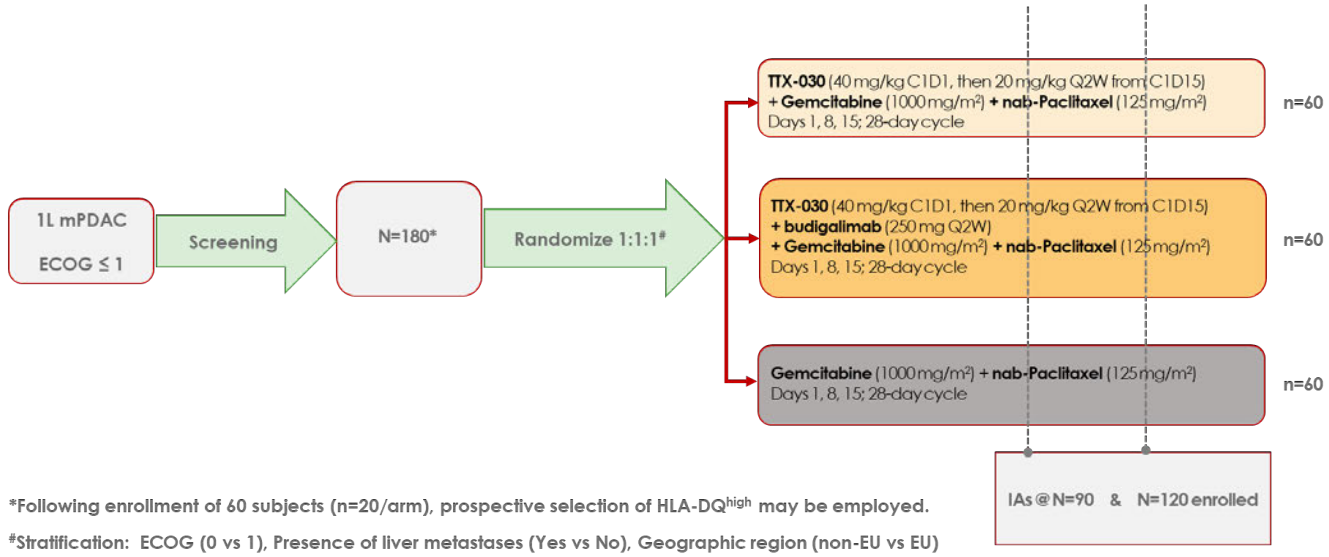
This is a Phase 2, multicenter, open-label, 3-arm, randomized, parallel group study to evaluate the efficacy and safety of TTX-030 with or without budigalimab in combination with chemotherapy (gemcitabine + nab-paclitaxel) in subjects with metastatic PDAC who did not have prior treatment for metastatic disease and are eligible to receive gemcitabine and nab-paclitaxel chemotherapy as SOC.

The study will enroll and randomize approximately 180 subjects (n = 60/arm) with a target enrollment of a minimum of 120 HLA-DQ^{high} subjects (n ≥ 40/arm). Subjects will be randomized 1:1:1 to one of the following 3 treatment arms:

- Arm 1: TTX-030 + nab-paclitaxel + gemcitabine
- Arm 2: TTX-030 + budigalimab + nab-paclitaxel + gemcitabine
- Arm 3: Nab-paclitaxel + gemcitabine

The study schema is depicted in Figure 1.

Figure 1: Study Schema



1L=first line; C=Cycle; D=Day; ECOG=Eastern Cooperative Oncology Group; HLA-DQ^{high}=high expression level of HLA-DQ at baseline; IA=interim analysis; mPDAC=metastatic pancreatic ductal adenocarcinoma; Q2W=every 2 weeks.

1.2. Study Objectives and Endpoints

Type	Objectives	Endpoints
Primary		
Efficacy	• To evaluate the benefit of the addition of TTX-030 with or without budigalimab to nab-paclitaxel + gemcitabine in the HLA-DQ^{high} population	• PFS
Secondary		
Efficacy	• To evaluate the benefit of the addition of TTX-030 with or without budigalimab to nab-paclitaxel + gemcitabine in the overall population and in the HLA-DQ^{high} population	• PFS, ORR, DoR, OS
Safety	• To evaluate the safety profile observed with the addition of TTX-030 with or without budigalimab in combination with nab-paclitaxel + gemcitabine	• Type, severity, and frequency of treatment-emergent AEs
Exploratory		
Pharmacokinetics	• To describe the PK profiles of TTX-030 and budigalimab	• Serum concentrations and PK parameters
Antidrug antibody	• To describe the immunogenicity of TTX-030 and budigalimab	• Number and percentage of subjects who develop ADA
Pharmacodynamics	• To assess the effects of TTX-030 with or without budigalimab on pharmacodynamic biomarkers in peripheral blood and tumor tissue	• Exploratory pharmacodynamic biomarkers and correlatives

ADA=antidrug antibodies; AE=adverse event; DoR=duration of response; HLA-DQ^{high}=high expression level of HLA-DQ at baseline; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetics

1.3. Sample Size

The planned sample size is 180 subjects (60 subjects per treatment arm) with a goal of enrollment of approximately 120 HLA-DQ^{high} subjects (40 per treatment arm). After the first 60 subjects are enrolled, prospective selection of HLA-DQ^{high} subjects may be employed subsequently. The expected prevalence of HLA-DQ^{high} in all enrolled subjects is estimated to be ≥ 65%.

The treatment arms include:

- Arm 1: TTX-030 + nab-paclitaxel + gemcitabine
- Arm 2: TTX-030 + budigalimab + nab-paclitaxel + gemcitabine
- Arm 3: nab-paclitaxel + gemcitabine

With a total of 54 PFS events from the SOC arm (Arm 3) and 1 experimental arm including treatment with TTX-030 (Arm 1 or 2) in HLA-DQ^{high} subjects, the study has 80% power to detect a hazard ratio (HR) of 0.56 at a 1-sided 0.10 significance level. No multiplicity will be adjusted for this Phase 2 proof of concept study. Statistical significance (at 1-sided alpha of 0.1)

for PFS will occur with an observed HR=0.706 with 54 PFS events, corresponding approximately to a 41.6% increase in observed median PFS (e.g., from 6 months to 8.5 months).

2. TYPE OF PLANNED ANALYSES

2.1. Interim Safety Evaluation

An evaluation of toxicity in the investigational treatment arms (Arm 1 and Arm 2) will be performed when 6 subjects per arm (18 subjects total) and 30 subjects per arm (up to 90 subjects total) are enrolled with a minimum of 28 days of follow-up. Toxicity will be defined as the following investigational treatment-related adverse events that occur during Cycle 1:

1. Grade ≥3 adverse events with the exception of:
    a. Nausea, vomiting or diarrhea that resolves with supportive care within 72 hours
    b. Laboratory findings without other clinical sequelae
    c. Laboratory findings that are reversible within 72 hours with standard of care management
2. Adverse events that lead to treatment discontinuation

Toxicity will be monitored in the study using Bayesian Optimal Phase 2 (BOP2) design (Zhou et al. 2017). Table 2 provides an example of toxicity stopping boundaries of the BOP2 design. If the stopping boundary is crossed in either investigational treatment arm, the accrual of that arm will be held, and the DMC will review the totality of safety, tolerability, PK and efficacy data to assess risk and benefit from the investigational treatment. All data observed in the control arm will also be considered in the review to provide a more complete and reliable assessment.

Table 2: Optimized Toxicity Stopping Boundaries

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[redacted]	[redacted]
[redacted]	[redacted]

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2.2. Interim Futility Analysis

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2.3. Final Analysis

The final analysis will take place when approximately 54 PFS events are recorded from the SOC arm (Arm 3) and 1 experimental arm (Arm 1 or 2) in the HLA-DQ^{high} subjects.

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 ITT Analysis Set and sorted by 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. Intent-to-Treat (ITT) Analysis Set

The Intent-to-Treat (ITT) Analysis Set consists of all subjects who are randomized in the study. The Intent-to-Treat Analysis Set will be used for subject disposition, baseline characteristics, and the primary analysis of efficacy endpoints.

3.1.2. ITT Analysis Set – HLA-DQ^{high}

The ITT Analysis Set – HLA-DQ^{high} consists of all subjects in the ITT Analysis Set whose HLA-DQ status is high. The Intent-to-Treat Analysis Set will be used for subject disposition, baseline characteristics, and primary analysis of efficacy endpoints for subjects whose HLA-DQ status is high.

3.1.3. 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.

3.1.4. Efficacy-Evaluable Analysis Set

The Efficacy-Evaluable Analysis Set includes all subjects in the ITT Analysis Set who received any study treatment (including any partial dose) and had at least 1 postbaseline evaluable tumor assessment or death occurred prior to the first post baseline disease assessment.

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

3.1.5. Futility Analysis Set

3.1.5.1. Futility Analysis Set 1

The Futility Analysis Set 1 includes the first 90 subjects in the ITT Analysis Set. The Futility Analysis Set 1 will be only used for the summary of ORR in the first futility analysis.

3.1.5.2. Futility Analysis Set 2

The Futility Analysis Set 2 includes the first 120 subjects in the ITT Analysis Set. The Futility Analysis Set 2 will be only used for the summary of ORR in the second futility analysis.

Table 4. Analysis Sets Used for the Endpoints

	ITT	ITT Analysis Set – HLA-DQ^{high}	Efficacy-Evaluable Analysis Set	Safety Analysis Set	Futility Analysis Set 1	Futility Analysis Set 2	Subgroup Analysis
OS	Primary	Secondary					Y
PFS	Secondary	Primary					Y
ORR	Secondary	Primary	Sensitivity		Y	Y	HLA-DQ Status & HLA-DQ Genotype DQA1*01
DOR	Secondary	Primary					
AE				Primary			

3.2. Subject Grouping

Subjects will be grouped according to the actual treatment they received.

3.3. Stratification Factors

Subjects were randomized 1:1:1 to one of the three treatment arms, stratified based on the following factors:

- ECOG (0 vs 1)
- Presence of liver metastases (Yes vs No)
- Geographic region (non-EU vs EU)

Geographic region was added as a stratification factor in the middle of the trial in preparation of prospective selection for HLA-DQ status in different regions. Prospective selection for HLA-DQ status was not implemented in this study, therefore will not be used in the stratified statistical analyses as outlined in 6.

If there are discrepancies in stratification factor values between the interactive voice or web response system (IXRS) and the clinical database, the values recorded in the clinical database will be used for analysis.

Stratified analyses for efficacy endpoints will be performed with the stratification factors. In the situation where there is insufficient information in a stratum (i.e. if there are <10 subjects or there are no informative events in a stratum), pooling of the stratum with the smallest adjacent stratum for stratified analyses will be considered; the smallest stratum is defined as the stratum having the fewest number of subjects or the fewest number of events in case the former is a tie and the adjacent stratum is defined as a stratum having 1 factor of the 2 at the same level.

3.4. 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)
- ECOG (0; 1)
- Presence of liver metastasis (yes; no)
- RT qPCR HLA-DQ status (HLA-DQ^{high}; HLA-DQ^{low})
- HLA-DQ genotype
    - DQA1*01: presence; absence
    - DQB1*05/06: presence; absence. Note that in the event DQB1*05/06 identifies a similar set of subjects (e.g. ≤10 discordance pairs) as DQA1*01, only the subgroup analysis by DQA1*01 will be done.

Definitions of HLA-DQ subgroups are provided in Section 5.5.

3.5. Multiple Comparisons

No multiplicity adjustments will be made in this study.

3.6. Missing Data and Outliers

3.6.1. 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 is described in Section 5.3; prior anticancer therapy in Section 5.4.1; for prior and concomitant medications in Section 5.4; for new anticancer therapy is described in Section 6.1, for AE onset is described in Section 7.1.5.

3.6.2. 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.

3.7. 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.

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

For efficacy endpoints, study day will be calculated from the date of randomization:

- Post-Randomization Study Days = Assessment Date – Randomization Date + 1
- Study Day prior to Randomization = Assessment Date – Randomization Date

For safety endpoints, study day will be calculated from the first dose date:

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

3.8.2. Analysis Visit Windows

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

3.8.3. Selection of Data

In general, unless specified otherwise, the baseline value for efficacy endpoints will be the last non-missing value on or prior to the date of randomization; the baseline value for safety endpoints will be the last non-missing value on or prior to the first dose date. For efficacy endpoints, if there is no non-missing value on or prior to the date of randomization, the baseline value will be the last non-missing value on or prior to the first dose date.

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 worst severity will be considered the baseline value.

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
- Randomization
- 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, nab-paclitaxel, and gemcitabine):

- 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 and budigalimab: (last available dosing date – first dosing date + 14) / 7
- Gemcitabine and Nab-paclitaxel: (last available dosing date – first dosing date + 7) / 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, or infusion 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 ITT Analysis Set. The demographic characteristics include age, sex, race and ethnicity.

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 ITT 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 randomization – date of initial diagnosis) / 30.4375. They will be summarized using summary statistics for a continuous variable. Disease stage at diagnosis 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 start date.

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 ITT 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.

5.5. HLA-DQ Expression

5.5.1. HLA-DQ Genotype

HLA-DQ genotype will be assessed by testing at a central lab.

5.5.1.1. HLA-DQA1*01

DQA1*01 presence is defined as the presence of at least one DQA1*01 allele in one of the two DQA1 alleles. Details are provided in Table 5.

Table 5. DQA1*01

		Allele 2		
		DQA1*01	**No DQA1*01**	**Not Reported**
Allele 1	**DQA1*01**	Presence	Presence	Presence
	No DQA1*01	Presence	Absence	NA
	Not Reported	Presence	NA	NA

5.5.1.2. HLA-DQB1*05/06

DQB1*05/06 presence is defined as the presence of at least one DQB1*05 or DQB1*06 allele in one of the two DQB1 alleles. Details are provided in Table 6.

Table 6. DQB1*05/06

		Allele 2			
		DQB1*05	**DQB1*06**	**No DQB1*05/06**	**Not Reported**
Allele 1	**DQB1*05**	Presence	Presence	Presence	Presence
	DQB1*06	Presence	Presence	Presence	Presence
	No DQB1*05/06	Presence	Presence	Absence	NA
	Not Reported	Presence	Presence	NA	NA

5.5.2. HLA-DQ RT-qPCR

HLA-DQ expression will be assessed by quantitative reverse transcript polymerase chain reaction (RT-qPCR) at a central lab.

5.5.2.1. HLA-DQ^{high}

HLA-DQ expression level are assessed for being above or below the cycle threshold (Ct) threshold for both DQA1 and DQB1. HLA-DQ^{high} is defined as being below the chosen Ct of the RT-qPCR assay result for either of the two genes (DQA1 or DQB1). Details of HLA-DQ status are provided in Table 7.

Table 7. HLA-DQ^{high} vs. HLA-DQ^{low}

		DQB1		
		Detected	**Not Detected**	**NE**
DQA1	**Detected**	High	High	High
	Not Detected	High	Low	Low
	NE	High	Low	NE

6. EFFICACY ANALYSES

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

6.1. Overall Survival (OS)

Overall survival (OS) is the key efficacy endpoint of the study, defined as time from the date of randomization 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. Subjects with confirmed death or alive status after the data cutoff date will be censored at the data cutoff date.

Every attempt will be made to ensure that complete death dates are recorded. In those rare instances where complete death dates are not recorded, the following algorithm will be used:

- If date is missing but the month and year are available, then the imputed day will be the first day of the month or the last assessment date + 1, whichever is later.
- If day and month are missing but year is available, then the imputed day and month will be 01Jan or the last day of the latest month that the subject was known to be alive if they have the same year, whichever is later.

The primary hypothesis to be tested is that there is no difference in OS between the experimental arms (Arm 1 or Arm 2) and the control arm (Arm 3). Using $S_T(t)$ and $S_C(t)$ to denote the OS distribution functions of the experimental arms (Arm 1 or Arm 2) and the control arm (Arm 3), respectively, the statistical hypotheses to be tested in this study will be:

H_0: $S_T(t) = S_C(t)$

H_1: $S_T(t) > S_C(t)$

The primary analysis of OS will be performing using the Kaplan-Meier method for the ITT Analysis Set. The OS distribution of the experimental arms will be compared against the control arm using the stratified log-rank test, stratified by the stratification factors at randomization. Medians, Q1, Q3, the probability of being alive at 3, 6, 9 and 12 months from Study Day 1 will be provided along with corresponding 95% confidence intervals (CI). The unstratified log-rank test will also be performed. Kaplan-Meier (KM) curves will be provided by treatment group.

In addition, the hazard ratio (HR) between the two experimental arms and the control arm and the corresponding 95% CI will be estimated using the Cox proportional hazards regression model with treatment arm as the only main effect and stratified by the stratification factors at randomization.

Hazard ratios between the two experimental arms (Arm 1 vs Arm 2) will also be provided. Hazard ratios of the pooled experimental arm (Arm1 + Arm 2) against the control arm (Arm 3), will be provided if the hazard ratios from the pairwise comparison (Arm 1 vs Arm 3 and Arm 2 vs Arm 3) are both ≤0.80.

A listing will be provided for the information of subject OS.

OS analysis will also be performed for the ITT Analysis Set – HLA-DQ^{high}.

Sensitivity analyses will be done for the ITT Analysis Set, similar as described for the primary analysis, with an additional stratification factor in the model, either HLA-DQ status (high vs low) or HLA-DQ genotype DQA1*01 (presence or absence).

OS will also be analyzed by the subgroups, more specifically, HLA-DQ status (high and low), and the HLQ-DQ genotype (DQQ1*01 presence and absence). Same analysis as specified for the primary analysis will be performed, except that only the unstratified log-rank test will be provided and the hazard ratio estimated by the Cox proportional hazard model will not be stratified by randomization stratification factors.

6.2. Progression-Free Survival (PFS)

6.2.1. Definition of the Primary Efficacy Endpoint

Progression-free survival (PFS) is the primary efficacy endpoint, defined as time from the date of randomization 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 data. A clinical deterioration determined by an investigator will not be considered as a progression event. Data will be censored on the date of last adequate tumor assessment for subjects:

- who do not have disease progression or die prior to 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

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.

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.

The convention to be followed when assessing response or progression will be as follows:

- The date of response (CR, PR, SD or NE) will be recorded as the date of the last radiographic evaluation included in the same visit folder for that response assessment.

- The date of progression (PD) will be recorded as the date of the earliest radiographic evaluation included in the visit folder for that response assessment.

The primary hypothesis to be tested is that there is no difference in PFS between the experimental arms (Arm 1 or Arm 2) and the control arm (Arm 3), similar as described for the OS.

The primary analysis of PFS will be performing using the Kaplan-Meier method for the ITT Analysis Set – HLA-DQ^{high}. The analyses for PFS will be performed in a similar manner as described for OS.

A listing will be provided for the information of subject PFS.

PFS analysis will also be performed for the ITT Analysis Set.

As a sensitivity analysis, the Cox proportional regression model with treatment arm as the only main effect and stratified by the stratification factors and HLA-DQ status (high vs low). Similarly, comparisons of the OS distribution among the treatment arms will use the stratified log-rank test, stratified by the stratification factors at randomization as well as HLA-DQ status (high vs low).

Other sensitivity analyses may be explored, for example:

- PFS may be analyzed by considering clinical progression as a PFS event. The date of documented radiographic progression, clinical progression, or death, whichever is earlier, will be considered as PFS event date.
- PFS may be analyzed by considering initiation of new anticancer therapy as a PFS event. Furthermore, PFS will not be censored by having ≥2 consecutive missing tumor assessments before documented progression or death or initiation of new anticancer therapy.

PFS will also be analyzed based on the subgroups, more specifically, HLA-DQ status (high and low), and the HLQ-DQ genotype (DQA1*01 presence and absence). Same analysis as specified for the primary analysis will be performed, except that only the unstratified log-rank test will be provided and the hazard ratio estimated by the Cox proportional hazard model will not be stratified by randomization stratification factors.

6.3. Objective Response Rate (ORR)

Objective response rate (ORR) is defined as the proportion of subjects who achieve best overall response (BOR) of either complete response (CR) or partial response (PR) as assessed 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 the date of randomization until the end of study, first disease progression, death, or start of new anti-cancer therapy, or last documented assessment before ≥2 consecutive missing tumor assessments, 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. Confirmation of CR/PR is not required for the primary analysis.

The primary analysis of ORR will be performed for the ITT Analysis Set – HLA-DQ^{high}. ORR with corresponding 2-sided 95% CI based on Clopper-Pearson method along with each category of BOR will be summarized by treatment group. Patients who don't have any postbaseline adequate tumor assessments will be counted as non-responders. A conventional 2-sided 95% CI of the difference in ORR of two treatment groups and the corresponding p-value will be calculated based on stratum-adjusted Cochran-Mantel-Haenszel (CMH) proportions (Koch, Carr, Amara, Stokes & Uryniak, 1989):

$$\hat{p}_t - \hat{p}_c \pm Z_{1-\alpha/2} \cdot SE(\hat{p}_t - \hat{p}_c)$$

where

- $\hat{p}_t$ and $\hat{p}_c$ denote the response rate in the experimental arm (Arm 1or Arm 2) and the control arm (Arm 3), respectively.
- $\hat{p}_t - \hat{p}_c = \frac{\sum W_h d_h}{\sum W_h}$, where $d_h = \hat{p}_{th} - \hat{p}_{th}$ is the stratum-adjusted CMH proportion difference in stratum *h* (*h* = 1, 2, …, K).
- $W_h = \frac{n_{th} n_{ch}}{n_{th}+n_{ch}}$ is the weight based on the harmonic mean of sample size per treatment group for each stratum where n_{th} and n_{ch} are the sample sizes of each treatment group in stratum *h*.
- $SE(\hat{p}_t - \hat{p}_c) = \frac{\sqrt{\sum W_h^2 \left(\frac{\hat{p}^*_{th}\left(1-\hat{p}^*_{th}\right)}{n_{th}-1} + \frac{\hat{p}^*_{ch}\left(1-\hat{p}^*_{ch}\right)}{n_{ch}-1} \right)}}{\sum W_h}$, where $\hat{p}^*_{th} = \frac{m_{th}+0.5}{n_{th}+1}$, $\hat{p}^*_{ch} = \frac{m_{ch}+0.5}{n_{ch}+1}$, m_{th} and m_{ch} are the number of responders in stratum *h* of each treatment group.
- $Z_{(1-\alpha/2)}$ is the 100(1-α/2)th percentile of normal distribution, where α = 0.05.

For the interim futility analyses, the analysis of ORR will be performed for the Futility Analysis Set 1 and 2, overall and in the subgroup of HLA-DQ high and HLA-DQ genotype DQA1*01 presence.

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.

As a sensitivity analysis, confirmed ORR (i.e. confirmation of CR/PR) will be used. Determination of BOR with confirmation of CR/PR is shown in Table 8. 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 8. 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.

ORR analysis will also be performed for the ITT Analysis Set and Efficacy Analysis Set.

6.4. Duration of Response (DoR)

Duration of response (DoR) is defined as the time 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 will be evaluated using the investigator assessments based on subset of subjects in the ITT Analysis Set – HLA-DQ^{high} who achieve a response. DOR will be summarized using Kaplan-Meier methods (median, Q1, Q3 and the corresponding 95% CI).

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

In the analyses of DOR, data will be censored on the date of the last tumor assessment for subjects

- Who do not have documented progression or die, or
- Who start new anticancer therapy before documented progression or death without documented progression, or
- Who have ≥2 consecutive missing tumor assessments before documented progression or death without documented progression

DOR will be analyzed using the Kaplan-Meier method for the ITT Analysis Set – HLA-DQ^{high}. Medians, Q1, and Q3 will be provided along with corresponding 95% confidence intervals (CI). Kaplan-Meier (KM) curves will be provided by treatment group. DOR analysis will also be performed for the ITT Analysis Set.

6.5. Other Efficacy Endpoints

Not applicable.

6.6. Changes from Protocol-Specified Efficacy Analysis

Given the fast enrollment of the study, the 90th subject and 120th subject were randomized approximately one month apart. Thus the first and second interim futility analysis sets will be analyzed at the protocol-specified horizon of the potential for 2 scans (16 weeks) following the randomization of the 120th subject.

It was originally planned for the interim futility analyses to be conducted in the 3 HLA-DQ-enriched subgroups (40%, 50% and 60% upper expression level). The distribution of RT qPCR expression is consistent with the clustering of HLA-DQ status into two groups (high vs low) using the pre-specified cutoff point of cycle threshold (Ct). Therefore, the interim futility analyses will be performed solely by selecting subjects who have HLA-DQ status (high) instead.

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, budigalimab, 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 gemcitabine
- TEAE related to nab-paclitaxel
- TE SAE related to TTX-030
- TE SAE related to budigalimab
- TE SAE related to gemcitabine
- TE SAE related to nab-paclitaxel
- TEAE leading to TTX-030 treatment discontinuation
- TEAE leading to budigalimab treatment discontinuation
- TEAE leading to gemcitabine treatment discontinuation
- TEAE leading to nab-paclitaxel treatment discontinuation
- TEAE leading to death

- TE immune-related AE
- TE infusion-related reactions

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. Adverse Events of Special Interest

An AESI is an event of scientific and medical interest specific to understanding of the investigational product(s) and may require close monitoring and rapid communication by the Investigator to Trishula. An AESI may be serious or nonserious. The AESI for this study is cytokine release syndrome.

Cytokine release syndrome is a potentially severe immune reaction that may occur in response to immunotherapies. The largest risk factor is high tumor load. Symptoms may include high fevers, rigors, myalgia, headache, nausea, vomiting, malaise, hypotension, rash, dyspnea, hypoxia, and tachycardia. Elevations in serum aminotransferases and bilirubin can be seen, and, in some cases, disseminated intravascular coagulation, capillary leak syndrome, and a hemophagocytic lymphohistiocytosis-like syndrome may be seen.

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 prognostic effect of HLA-DQ on ORR, PFS and OS may be evaluated by comparing HLA-DQ high vs HLA-DQ low in Arm 3.

Additional analysis of pharmacodynamics 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.

10. SOFTWARE

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

11. APPENDICES

Appendix 1. Schedule of Assessments

Treatment Cycle (4-Week Cycles)	Screening	Baseline[a]	Cycle 1 (Days 1-28)			Cycle 2 (Days 29-56)			Cycles 3 to 24 (Days 57-672+)			EOT /Follow-Up	
Treatment Days for Each Cycle			**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**EOT Visit**	**FU Visit[u]**
Scheduling Window (Days)	**(-28 to -1)**	**(-3)**	**D1[a]**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**30 (±9) Days After Last Dose**	**Q12W (+4 W) After Last Dose**
Administrative Procedures/Assessments													
Informed consent	X												
Inclusion/Exclusion criteria	X												
Subject identification card	X												
Demographics and medical history	X												
Cancer disease and prior treatment details	X												
Randomization/IRT registration[a]		X											
Contraception check[b]	X	X	X	X	X	X		X	X		X	X	X
Prior and concomitant medications[c]	X	X	X	X	X	X		X	X		X	X	
Review adverse events[d]	X	X	X	X	X	X		X	X		X	X	X[v]
Subsequent anticancer therapy												X	X
Survival status													X
Clinical Procedures/Assessments													
Height	X												
Vital signs (temperature, HR, BP, weight)	X	X	X	X	X	X	X	X	X	X	X	X	
Full physical examination	X	X				X			X			X	
Symptom-directed examination			X		X			X			X		
ECOG performance status	X	X	X		X	X		X	X		X	X	
Triplicate 12-lead ECGs[e]	X												
MUGA/ECHO[f]	X[f]												
Laboratory Procedures/Assessments (Analyzed by Local Laboratory)													

Treatment Cycle (4-Week Cycles)	Screening	Baseline[a]	Cycle 1 (Days 1-28)			Cycle 2 (Days 29-56)			Cycles 3 to 24 (Days 57-672+)			EOT /Follow-Up	
Treatment Days for Each Cycle			**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**EOT Visit**	**FU Visit[u]**
Scheduling Window (Days)	**(-28 to -1)**	**(-3)**	**D1[a]**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**30 (±9) Days After Last Dose**	**Q12W (+4 W) After Last Dose**
Pregnancy Test – urine or serum HCG[g]	X		X			X			X			X[h]	
Hepatitis serology tests (HbsAg, anti-HBc, and anti-HCV)[i]	X												
CBC with differential	X	X	X	X	X	X	X	X	X	X	X	X	
Comprehensive chemistry panel[j]	X	X	X		X	X		X	X		X	X	
Coagulation profile (PT/INR, PTT or aPTT)	X	X	X			X			X			X	
Urinalysis		X	X			X			X			X	
Thyroid function tests[k]	X	X	X			X			X			X	
Pituitary function tests	X		X[l]										
Serum tumor associated marker (e.g., CA 19-9)	X		X			X			X			X	
PK/Pharmacodynamic Biomarker/Tumor Tissue Collection (Analyzed by Central Testing Laboratory)													
TTX-030 PK blood sample[m] (pre & post infusion on C1D1 until C9D1, then Q8W)			X	X	X[m]	X			Until C9D1 then Q8W			X	
Budigalimab PK blood sample[n] pre & post infusion on C1D1 until C9D1, then Q8W)			X	X		X			Until C9D1 then Q8W			X	
ADA blood sample/serum pharmacodynamic[o] pre infusion on C9D1 until C8DW)	X		X			X			Until C9D1 then Q8W			X	
Pharmacodynamic and correlative blood samples – plasma for ctDNA[o]	X		X			X			Q8W			X	
Pharmacodynamic and correlative blood samples – plasma[o]	X		X						Q8W until C7D1			X	

Treatment Cycle (4-Week Cycles)	Screening	Baseline[a]	Cycle 1 (Days 1-28)			Cycle 2 (Days 29-56)			Cycles 3 to 24 (Days 57-672+)			EOT /Follow-Up	
Treatment Days for Each Cycle			**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**EOT Visit**	**FU Visit[u]**
Scheduling Window (Days)	**(-28 to -1)**	**(-3)**	**D1[a]**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**30 (±9) Days After Last Dose**	**Q12W (+4 W) After Last Dose**
Pharmacodynamic and correlative blood samples – whole blood[o]	X		X										
Pharmacodynamic and correlative blood samples – proinflammatory cytokine panel[o]	X		X						Q8W until C5D1				
Tumor tissue collection[p]	X					X (-7D)							
Efficacy Measurements													
Tumor assessment[q]	X								Q8W (-7D)				Q8W (-9D) Post EOT[u,w]
Study Drug Administration													
TTX-030 Q2W (Arms 1 and 2)[r,s]			X		X	X		X	X		X		
Budigalimab Q2W (Arm 2)[s]			X		X	X		X	X		X		
Nab-paclitaxel + gemcitabine (Arms 1, 2, and 3)[r,s,t]			X	X	X	X	X	X	X	X	X		

ADA = antidrug antibody; aPTT =activated partial thromboplastin time; BP=blood pressure; CBC=complete blood count; C=Cycle; CA 19-9=cancer-related antigen 19-9; CT=computed tomography; D=Day; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=End of Treatment; FFPE=formalin-fixed paraffin-embedded; FSH=follicle-stimulating hormone; FU=Follow-up; HCG=human chorionic gonadotropin; HR=heart rate; INR=international normalized ratio; IRT=Interactive Response Technology; MRI=magnetic resonance imaging; MUGA=multigated acquisition; PET=positron emission tomography; PK=pharmacokinetics; PT=prothrombin time; PTT=partial thromboplastin time; Q2W=every 2 weeks; Q8W=every 8 weeks; Q12W=every 12 weeks; TSH=thyroid-stimulating hormone.

[a] Baseline and C1D1 assessments may be combined if they occur within 3 days prior to the first dose. Upon approval of enrollment, randomization/IRT registration is to occur within 3 days before the start of the first dose. For subsequent visits, assessments may be performed up to 3 days prior to dosing visit.
[b] Contraception is required until 6 months (180 days) after the last dose of any study treatment.
[c] Concomitant medication information is to be collected from 30 days prior to Screening through 30 days after the last dose of study treatment.
[d] Adverse events/serious adverse events irrespective of attribution to study treatment are to be collected from the time the subject provides written informed consent through 30 days after the last administration of study treatment or until initiation of a new systemic anticancer therapy, whichever occurs first.
[e] Triplicate 12-lead ECGs will be performed approximately 2 minutes (or 1 minute, if applicable) apart to determine mean QTc interval. Additional ECG and/or other cardiac monitoring during subject's study participation may be performed as medically indicated.
[f] MUGA/ECHO is required for subjects with history of congestive heart failure at Screening. A follow-up assessment will be obtained during the study as per the Investigator's discretion.
[g] Serum pregnancy test is required at Screening for women of childbearing potential; serum test and/or urine dipstick are required at subsequent visits. If a female subject's menstrual cycle has become irregular or she has not had her period, FSH test at Screening/Baseline is required to confirm (post-)menopausal status.
[h] Pregnancy testing should be performed monthly for 3 months following the last dose of TTX-030 or budigalimab.

[i] If hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody is positive, then PCR to quantify hepatitis B/C DNA must be performed and must be negative prior to randomization.

[j] The following analytes are required only at the Baseline visit: amylase, C-reactive protein, lactate dehydrogenase (LDH), lipase, and uric acid.

[k] T3 test to be performed as reflex for abnormal TSH/Free T4.

[l] Obtain only if not obtained at screening.

[m] For Arms 1 and 2: TTX-030 Pharmacokinetic (PK) sampling times must be documented by sites and will be captured in the database. Predose PK collection should occur 60 (±60) min prior to TTX-030 dosing. Post-dose PK should be collected 45 (±15) min after the end-of-infusion (EOI) of TTX-030. If using the same infusion filter line for PK draw, flushing is required. On C1D8, PK blood samples should be collected prior to dosing with nab-paclitaxel + gemcitabine. On C1D15, postdose collection is not required after TTX-030 infusion.

[n] For Arm 2: Budigalimab PK sampling times must be documented by sites and will be captured in the database. Budigalimab predose PK collection should occur 60 (±60) min prior to TTX-030 dosing and should be collected at the same time as the TTX-030 predose PK collection. Post-dose budigalimab PK should be collected 15 (±5) min after the end-of-infusion (EOI) (thru C8D1) and at 2 hours (±15 min) post infusion of budigalimab (only C1D1 and C3D1). If using the same infusion filter line for PK draw, flushing is required. On C1D8, PK blood samples should be collected prior to dosing with nab-paclitaxel + gemcitabine.

[o] ADA blood sample/serum pharmacodynamic and pharmacodynamic and correlative blood samples (serum, plasma, whole blood, and proinflammatory cytokine) should be collected prior to any dosing when applicable and occur at the same time as predose TTX-030 PK blood draws, when applicable.

[p] Eligible subjects are required to have adequate archival tissue obtained within 90 days prior to enrollment without treatment following the prior biopsy or a site of disease that is safely accessible for a biopsy to be performed. Biopsy of the primary site of disease in the pancreas or intrathoracic biopsies should not be performed to obtain tumor tissue for the purposes of this study. The optional on-study biopsy at C2D1 may only be performed if deemed safe by the Investigator. Please see Section 8.8 and the laboratory manual for additional details regarding biopsy requirements and collection.

[q] CT scans with contrast of the chest, abdomen, and pelvis are required for all subjects. Tumor assessments will include all known or suspected disease sites. Anatomic regions included in the CT scans should be per disease history and clinical symptoms (repeat the same CT series for all post-treatment tumor assessments as completed at Screening). If a subject is allergic to contrast agents for imaging, CT without contrast, MRI, or PET scans are allowed. The imaging modality and anatomic regions used must be uniform during study participation. Brain scans will be performed at Screening if disease is suspected and on study as appropriate to follow disease. See also Section 8.1. Tumor assessment should be repeated at the end-of-treatment visit if more than 6 weeks (±9 days) have passed since the last evaluation. All Screening and supplemental imaging must be submitted to the central imaging vendor.

[r] Arm 1: TTX-030 (40 mg/kg C1D1, then 20 mg/kg Q2W from C1D15) will be administered prior to nab-paclitaxel 125 mg/m^2 + gemcitabine 1000 mg/m^2 (Days 1, 8, and 15 each 28-day cycle). A minimum of 60 minutes wait time after the completion of TTX-030 infusion is required to monitor for potential infusion-related reactions.

[s] Arm 2: TTX-030 (40 mg/kg C1D1, then 20 mg/kg Q2W from C1D15) will be administered prior to budigalimab (250 mg Q2W). Budigalimab will be administered prior to nab-paclitaxel 125 mg/m^2 + gemcitabine 1000 mg/m^2 (Days 1, 8, and 15 each 28-day cycle). A minimum of 60 minutes wait time after the completion of each infusion is required to monitor for potential infusion-related reactions.

[t] Arm 3: Nab-paclitaxel 125 mg/m^2 + gemcitabine 1000 mg/m^2 (Days 1, 8, and 15 each 28-day cycle) will be administered in this arm.

[u] The first follow-up visit should occur no sooner than 12 weeks after the last dose of study treatment. Follow-up Visit assessments for subjects not receiving tumor assessment can be conducted remotely over the phone. The subsequent follow-up window is Q12W (±4W).

[v] Follow-Up Visits: Adverse event review should be performed at the first follow-up visit only and directed at those adverse events attributed to study treatment.

[w] Subjects who discontinue treatment for reasons other than documented disease progression will continue to undergo tumor assessments (~Q8W) until disease progression is documented, death, initiation of alternative anticancer treatment, withdrawal of consent for further follow-up, or lost to further follow up. Follow-up assessments can be conducted at the time of tumor assessment.

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