TITLE PAGE

Protocol 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
Protocol Number:	TTX-030-003
Experimental Products:	TTX-030, Budigalimab (ABBV-181)
Sponsor:	Trishula Therapeutics, Inc. 2268 Westborough Boulevard, Suite 302 #263 South San Francisco, CA 94080
Medical Monitor:	[redacted]
IND Number:	167615
EU CT Number:	2023-508356-19-00
Protocol Version, Date:	Version 2.0 (US, APAC), 13 June 2024

CONFIDENTIAL

PROTOCOL APPROVAL PAGE

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Approval of Protocol by Sponsor:

[redacted]
Chief Medical Officer

PROTOCOL ACCEPTANCE FORM

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By my signature below, I hereby state that I have read and agree to abide by the instructions, conditions, and restrictions of the protocol, in accordance with Good Clinical Practice guidelines, the Declaration of Helsinki, and all applicable laws and regulations.

_____ _____

Name of Investigator (print) Name of Investigator (signature)

_____

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Version 1.0, Original Protocol	16 August 2023
Version 1.1, IND Response	18 September 2023
Version 2.0, US, APAC Version	13 June 2024

Amendment Version 2.0 US, APAC Version (13 June 2024)

Significant changes in Version 2.0 (US, APAC) of the TTX-030-003 protocol compared with Version 1.1 are summarized below. Editorial and administrative changes are made throughout the document to improve clarity and reduce duplication and do not substantively change the study design or conduct

Overall Rationale for the Amendment:

Section #	Description of Change	Brief Rationale
Section 1.1; Section 5.2	Addition of exclusion criterion #13 of concurrent malignancy.	Protocol prohibits non-study cancer treatment.
Section 1.1; Section 5.1	Addition of inclusion criterion (#15 of HLA-DQ^{high} status once prospective selection implemented.	Explicit statement of biomarker requirement once prospective selection is employed.
Section 1.1, Section 6.3.2	Added region as a stratification variable.	To control for region-specific variation in patient characteristics and outcomes.
Section 1.1; Section 1.3 (footnote p); Section 5.1; Section 8.8	Clarification that fresh biopsies of the primary site of disease in the pancreas or intrathoracic biopsies should not be performed for the protocol-specified tissue requirements.	To ensure that high-risk biopsy sites are not used (limit patient risk).
Section 1.1; Section 1.2; Section 4.1.1; Section 6.3.1; Section 10.1	Revised biomarker testing plan to specify that prospective selection for HLA-DQ status may begin after a minimum of 60 subjects are enrolled.	Increase in flexibility to switch to prospective enrollment to ensure an adequate number of HLA-DQ^{high} subjects are enrolled.
Section 1.3, Section 8.2.6	Removed the pregnancy test assessment at Baseline.	Assessment already performed at Screening and Cycle 1 Day 1.
Section 1.3	Addition of serum tumor marker collection at Cycle 1 Day 1.	Provides the most appropriate baseline measurement for longitudinal monitoring.

Section #	Description of Change	Brief Rationale
Section 1.3	Updated frequency of collection of PK, ADA, and pharmacodynamic biomarker sampling.	Ensures adequate longitudinal sampling.
Section 1.3	Addition of pharmacodynamic biomarker sampling at Screening Visit.	Allows assessment of baseline intra-patient variability of biomarkers.
Section 1.3; Section 8.2.6 – Table 8	Clarification of collection of laboratory parameters: amylase, aPTT, C-reactive protein, lactate dehydrogenase (LDH), lipase, and uric acid	Allows for alternative use of aPTT (vs. PTT); clarification that remainder of laboratory parameters are only required at baseline (for potential comparison if needed on study).
Section 1.3 (footnote h)	Addition of pregnancy testing monthly for 3 months following last dose of TTX-030 or budigalimab.	Ensures surveillance through study drug washout.
Section 1.3, Section 8.1	Clarified types of scans to be performed at screening if disease is suspected (changed brain and bone scans to brain scans)	Removes bone scan as it is not applicable to the disease under study.
Section 1.3; Section 8.3.1	Clarified all AEs collected through EOT visit and that AEs attributed to study treatment collected through first Follow-Up visit.	Ensures systematic AE collection during the study and through study drug washout period.
Section 1.3; Section 8.8	Clarification that C2D1 biopsy is optional.	Addresses ambiguity around requirement of assessment to ensure that risk to patient is minimized.
Section 5.1	Updated inclusion criteria regarding age at the time of Screening for South Korea from ≥18 to >18.	Addresses country-specific requirement.
Section 6.5.1	Clarified that treatment modifications for each study drug should be considered independently for treatment modifications.	Allows flexibility in management of toxicities, which may be managed based on known toxicities of each treatment.
Section 6.5.1.3	Clarified that management of toxicities associated with nab-paclitaxel and gemcitabine should be according to Institutional standard of care and	Allows sites to manage toxicities according to the Institutions standard of care.

Section #	Description of Change	Brief Rationale
	that no interval between doses should be shorter than 1 week.	
Section 8.2.1	Clarified type of information to be collected as part of medical history.	Improves clarity.
Section 8.3; Section 12.4	Removed duplication and erroneous reference to the Safety Notification Form; consolidated guidance around safety reporting in Section 12.4.	Improves clarity and corrected error.
Section 8.8	Added additional information regarding diagnostic assay for HLA-DQ biomarker levels.	Clarifies process of eligibility determination in the prospective enrollment phase of the clinical study. Provided additional information about the investigational device used for determining HLA-DQ status.
Section 8.9	Clarification that samples will be anonymized after study completion, may be stored for up to 15 years after study completion, and removed duplicated language.	Improves clarity and transparency around sample management.
Section 10.4	Added rationale for using ORR for futility analysis.	If data maturity precludes use of PFS (primary endpoint) – study design including futility analysis remains unchanged.
Section 12.5.2.2	Added detailed contact information for expedited reporting of pregnancy.	Contact information was previously not in protocol.

1. PROTOCOL SUMMARY

1.1. Synopsis

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

Study Identifier: TTX-030-003

Study Design: Phase 2, multicenter, 3-arm, randomized, open-label, parallel group study

Name of Sponsor: Trishula Therapeutics, Inc.

Name of Investigational Agents: TTX-030 (anti-CD39 antibody), budigalimab (anti-PD-1 antibody)

Combination Chemotherapy and Active Comparator: Nab-paclitaxel/Gemcitabine

Study Schema: The study schema is provided in Section 1.2.

Number of subjects planned: Total of ~180 subjects (~60 subjects per treatment arm)

Study Sites Planned: Total of approximately 70 sites globally.

Objectives and Endpoints:

Type	Objective(s)	Endpoint(s)
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 concentration 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=anti-drug 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=pharmacokinetic.

Target Population: Adult subjects with histologically or cytologically confirmed diagnosis of metastatic pancreatic ductal adenocarcinoma, who did not have prior treatment for metastatic disease and are eligible to receive nab-paclitaxel + gemcitabine as standard of care (SOC).

Key eligibility criteria:

- Disease History:
  - Histologically or cytologically confirmed diagnosis of metastatic pancreatic ductal adenocarcinoma
  - Evidence of measurable disease using Response Evaluation Criteria in Solid Tumors v1.1 (RECIST 1.1)
  - No evidence of active central nervous system (CNS) metastatic disease or carcinomatous meningitis
  - No active disease requiring systemic treatment with either corticosteroids (>10 mg daily prednisone or equivalent) or other immunosuppressive medications within 14 days prior to Day 1 of treatment.
  - No history of autoimmune disease (e.g., including but not limited to rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, non-infectious pneumonitis, interstitial lung disease (ILD)) requiring systemic treatment or transplant that requires systemic steroids or immunosuppressive agents within the last 2 years.
  - No history of any other malignancy within the past 3 years except for: curatively treated carcinoma in situ; localized nonmelanoma or early-stage melanoma skin cancer; Stage 1 uterine cancer or localized prostate cancer that is considered adequately treated by the Investigator. Subjects with hematologic malignancies and anticipated overall survival (OS) of >5 years may be considered for enrollment but should be discussed with the Medical Monitor prior to evaluation.
  - Appropriate for treatment with nab-paclitaxel + gemcitabine.
  - Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1
- Prior treatment:
  - No prior systemic treatment for metastatic disease. Prior neoadjuvant or adjuvant systemic chemotherapy is permitted in the absence of disease progression within 6 months following last dose of chemotherapy.
  - No prior treatment with therapeutics specifically targeted to enhancing or de-repressing anti-tumor immunity including but not limited to checkpoint inhibitors or agents targeting the adenosine pathway (cluster of differentiation [CD]39, CD73, or adenosine receptor inhibitors)
- Tumor tissue samples:
  - Availability of tumor tissue (obtained by biopsy during Screening, or archival if collected within 90 days prior to first dose and in the absence of intervening therapy). 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. Subjects with contraindication for a biopsy procedure and without acceptable archival tissue samples are not eligible (Section 8.8).

- Required baseline laboratory test results as defined below:
  - Hematology: absolute neutrophil count (ANC) ≥1.2 k/μL, platelets ≥100 k/μL, hemoglobin (Hgb) ≥9 g/dL
  - Coagulation: prothrombin time (PT) and International Normalized Ratio (INR) ≤1.2 x upper limit of normal (ULN), except for subjects receiving anticoagulation; subjects must be on a stable dose of warfarin for 6 weeks prior to enrollment.
  - Kidney: creatinine clearance (CrCl) or estimated glomerular filtration rate (eGFR) ≥40 mL/min as calculated by Cockcroft-Gault or CKD-EPI
  - Liver: aspartate aminotransferase (AST), alanine aminotransferase (ALT) ≤2.5 x ULN (or ≤5 x ULN with hepatic metastases); total bilirubin ≤2 x ULN (or ≤3 x ULN with Gilbert's syndrome); serum albumin ≥3.0 g/dL

- No uncontrolled intercurrent illness including, but not limited to:
  a) Uncontrolled diabetes
  b) New York Heart Association Class 3 or Class 4 congestive heart failure
  c) Unstable angina, arrhythmia, or myocardial infarction within 6 months prior to Screening
  d) Poorly controlled hypertension, defined as a blood pressure consistently above 160/90 mmHg despite optimal medical management
  e) Uncontrolled pleural effusion, pericardial effusion, or ascites requiring repeated drainage more than once every 28 days. Indwelling drainage catheters (e.g., PleurX®) are allowed.
  f) Active or chronic viral hepatitis B or C infection
  g) Uncontrolled thyroid disease
  h) Active infection requiring systemic therapy, subjects receiving ongoing systemic antibiotic, antiviral or antifungal therapy for maintenance should be discussed with the medical monitor prior to Screening and enrollment

The following Inclusion Criterion is applicable once prospective selection has been implemented:

- Fresh or archival tumor tissue with HLA-DQ^{high} biomarker status per central laboratory testing.

Study procedures/visit frequency: See Schedule of Activities (Section 1.3).

Treatment arms and dosing schedules: Study subjects will be randomized at a 1:1:1 ratio to 2 experimental treatment arms (Arms 1 and 2) and the chemotherapy only comparator arm (Arm 3). Each treatment cycle is comprised of 28 days.

- **Arm 1:** TTX-030 (40 mg/kg cycle [C]1 day [D]1, then 20 mg/kg every 2 weeks [Q2W] from C1D15). Nab-paclitaxel (125 mg/m^2) + gemcitabine (1000 mg/m^2) will be administered on Days 1, 8, and 15. On days with concomitant infusion of TTX-030 and nab-paclitaxel + gemcitabine, TTX-030 will be administered before nab-paclitaxel/gemcitabine with an observation time of at least 60 minutes before start of the next infusion.
- **Arm 2:** In addition to TTX-030 and nab-paclitaxel + gemcitabine, subjects will receive budigalimab (250 mg Q2W) on Days 1 and 15 of every cycle. The order of infusions will be: TTX-030, followed by budigalimab, then nab-paclitaxel + gemcitabine (after an observation time of at least 60 minutes after TTX-030 and budigalimab)
- **Arm 3:** Nab-paclitaxel + gemcitabine will be administered on Days 1, 8, and 15

Enrollment and randomization:

The study will enroll and randomize approximately 180 subjects (n=60/arm) with a target enrollment of 120 HLA-DQ^{high} subjects in total (n=40/arm). A minimum of 60 subjects (n=20/arm) will be enrolled irrespective of tumor expression level of HLA-DQ. Prospective selection of subjects for tumor HLA-DQ^{high} status may be employed subsequently.

Stratification:

1. ECOG (0 vs 1)
2. Presence of liver metastases (yes vs no)
3. Geographic region (non-EU vs EU)

Duration of study treatment: The duration of study treatment is up to a maximum of 24 months from C1D1 or until disease progression, intolerable toxicity, or death, whichever occurs first. If a subject discontinues any of the combination agents due to intolerance, then treatment with the remaining combination components may continue. Once subjects discontinue/complete the study treatment period, they will enter the post-treatment Follow-up Phase and complete the required follow-up assessments as described per protocol.

Statistical considerations

Sample size

The planned sample size is 180 subjects (60 subjects 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 TTX-030 arm (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).

Interim analyses (IA) for futility

- Two interim analyses (IAs) for futility are planned at n=90 and n=120 total subjects enrolled with a minimum of 2 scans follow-up [~16 weeks].
- Overall futility principle: Futility at each interim analysis will be declared if the posterior predictive probability of a no-go decision at the final analysis is ≥94% for both experimental treatment arms in 3 HLA-DQ-enriched subgroups (40%, 50%, and 60% upper expression level).
  - Decision rule at the final analysis: If posterior probabilities of the true difference of objective response rates (p_t is ORR in one treatment arm and p_c is ORR in the control arm [for both treatment arms]) in all comparisons are:
    - $PP(p_t - p_c > 0.1|D) < 0.65$
      and
    - $PP(p_t - p_c > 0.2|D) < 0.1$

  Then results will be considered a no-go.

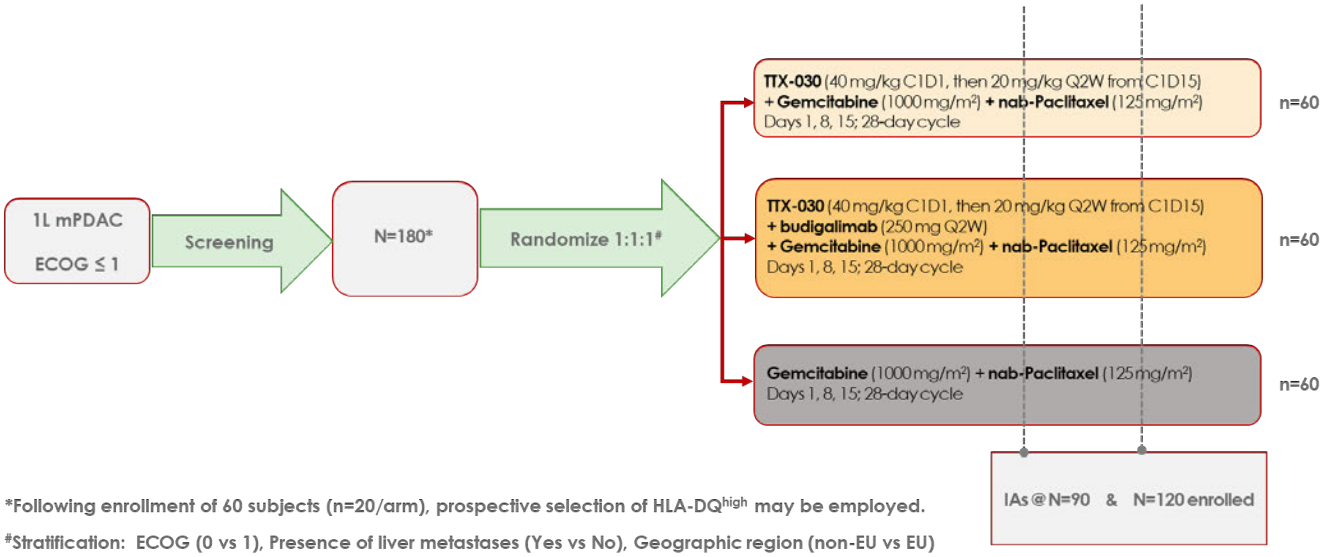
  The posterior probability will:
    - Primarily be based on observed data from 40 HLA-DQ^{high} subjects in each arm
    - Use partial historical information (15% weight). The historical information assumes 57% and 33% response rates in treatment and control groups, respectively, in the enriched portion with a total weight (i.e., sample size) of N=21 in each group.

- Implementation: Based on the decision rule at the final analysis, simulations indicate that futility at each IA would be declared if ≥3 fewer responses occurred in the treatment arms than control arm.
- Operating characteristics: Assuming the first and second interim analyses are conducted at ~15 HLA-DQ^{high} and ~20 HLA-DQ^{high} subjects per arm, respectively, and in both cases, the true underlying control group rate is 30%, the chance of futility is about 23% when there is no true difference in the response rates in the treatment and control groups. When the true difference is 10% or 20%, the chance of futility drops to ~9% or ~2.5%, respectively.

1.2. Study Schema

The study schema is presented 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.

1.3. Schedule of Activities

Detailed procedures/assessments to be performed starting from Screening to End-of-study are presented in Table 1.

Table 1: Schedule of Activities During Screening Through End of Study

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]												

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**
Laboratory Procedures/Assessments (Analyzed by Local Laboratory)													
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 C1D1 until C9D1, then Q8W)	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)[r,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. Postdose 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. Postdose budigalimab PK should be collected 15 (±5) min after the end-of-infusion (EOI) (thru C9D1, then Q8W) 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.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: Abbreviations

1L	first line
$A_{2a}R$	adenosine 2a receptor
ACTH	adrenocorticotropic hormone
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATP	adenosine triphosphate
C	cycle
CA 19-9	cancer-related antigen 19-9
CAP	College of American Pathologists
CD	cluster of differentiation
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete response
CRC	colorectal cancer
CrCl	creatinine clearance
CT	computed tomography
D	day
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DoR	duration of response
DRESS	drug reaction with eosinophilia and systemic symptoms
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form

EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOI	end of infusion
EOT	end of treatment
FFPE	formalin-fixed paraffin-embedded
FOLFIRINOX	5-FU, leucovorin, irinotecan, and oxaliplatin
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GEC	gastroesophageal cancer
Gem	gemcitabine
GH	growth hormone
Hgb	hemoglobin
HIV	human immunodeficiency virus
HLA-DQ^{high}	high expression level of HLA-DQ at baseline
HLA-DQ^{low}	low expression level of HLA-DQ at baseline
HNSCC	head and neck squamous cell carcinoma
HR	hazard ratio
IA	interim analysis
Ig	immunoglobulin
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFN	interferon
Ig	immunoglobulin
IHC	immunohistochemistry
IL	interleukin
ILD	interstitial lung disease
IMP	investigational medicinal product
INR	International Normalized Ratio
IP	investigational product
irAE	immune-related adverse event
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUO	investigational use only

IV	intravenous(ly)
LA	locally advanced
LDH	lactate dehydrogenase
LH	luteinizing hormone
mPDAC	metastatic pancreatic ductal adenocarcinoma
MRI	magnetic resonance imaging
MUGA	multigated acquisition
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	not estimable
NIMP	non-investigational medicinal product
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death-1
PD-L1	programmed cell death ligand-1
PDAC	pancreatic ductal adenocarcinoma
PET	positron emission tomography
PFS	progression-free survival
PI	package insert
PK	pharmacokinetic(s)
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAC	Scientific Advisory Committee
SAE	serious adverse event

SD	stable disease
SJS	Steven-Johnson syndrome
SOC	standard of care
SRD	Study Risk Determination
TEAE	treatment-emergent adverse events
TEN	toxic epidermal necrolysis
Trishula	Trishula Therapeutics, Inc.
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States

2. INTRODUCTION

2.1. Study Rationale

The aim of this study is to explore and characterize the properties of TTX-030, a cluster of differentiation (CD)39 inhibitor, in combination with other agents including the programmed cell death-1 (PD-1) inhibitor budigalimab (also known as ABBV-181) and chemotherapy in metastatic pancreatic ductal adenocarcinoma (mPDAC).

2.2. Background

2.2.1. Background on Pancreatic Adenocarcinoma

Worldwide, approximately 458,918 new cases and 432,242 deaths related to pancreatic cancer were estimated in 2018 (Bray et al, 2018). In the United States (US), approximately 64,050 new cases and 50,550 deaths related to pancreatic cancer are estimated in 2023 (Siegel et al, 2023).

Standard treatment for unresectable and metastatic pancreatic ductal adenocarcinoma currently includes first-line combination regimens of FOLFIRINOX (5-FU, leucovorin, irinotecan and oxaliplatin) or the combination of nab-paclitaxel with gemcitabine. Recently, substitution of liposomal irinotecan in a modification of the FOLFIRINOX regimen has also shown promising results in a Phase 3 study. With approved combinations, median overall survival (OS) for subjects diagnosed with metastatic disease continues to be less than 1 year, highlighting the need for better treatment options (NCCN Guidelines Pancreatic Adenocarcinoma, 2022; Santomasso et al, ASCO 2021; Sidaway 2023).

While immune checkpoint inhibitors have improved outcomes for subjects with a range of solid tumors, studies in pancreatic ductal adenocarcinoma (PDAC) have shown variable results with the clearest benefit derived by subjects with tumors having high microsatellite instability or deficient mismatch repair (Weiss et al, 2018; Padrón et al, 2022; O'Reilly et al, 2019). A number of studies combining anti-PD-1 antibodies with standard of care (SOC) chemotherapy are currently ongoing and innovative combinations increasing the potential benefit of anti-tumor immunity are needed to improved outcomes for subjects with pancreatic adenocarcinoma.

2.2.2. Background on TTX-030

2.2.2.1. CD39 and TTX-030

The adenosine triphosphate (ATP)-adenosine pathway is a key modulator of immune function. CD39 is an ectoenzyme responsible for converting ATP to adenosine diphosphate, the first step in a cascade that generates adenosine in the tumor microenvironment. Extracellular ATP released by dying or stressed cells functions as a pro-inflammatory signal critical for effective innate and adaptive immunity. Conversely, extracellular adenosine suppresses T cell and myeloid cell activity. Inhibition of CD39 leads to an increase in extracellular ATP and decrease in extracellular adenosine; both these effects have the potential to enhance anti-tumor immunity.

TTX-030 is a novel, fully human anti-CD39 antibody that inhibits CD39 ATPase enzymatic function allosterically with sub-nanomolar affinity and potency. [redacted]

[redacted]

Please refer to the TTX-030 Investigator's Brochure for more information.

2.2.2.2. Summary of Nonclinical Experience With TTX-030

TTX-030 is specific to CD39 and does not bind to other ectonucleoside triphosphate diphosphohydrolase family member proteins. Trishula Therapeutics, Inc. (hereafter referred to as Trishula or Sponsor) has conducted studies demonstrating that TTX-030 binds to $CD39^+$ cancer cell lines and primary human and cynomolgus monkey monocytes and T cells with high affinity. TTX-030 specifically and potently inhibits CD39-driven processing of ATP by tumor and immune cells and by $CD39^+$ tumor tissues, as demonstrated by a tumor tissue slice immunohistochemistry (IHC) assay. In addition to preserving pro-inflammatory ATP by inhibiting CD39 ATPase activity, TTX-030 inhibits downstream adenosine production, (e.g., in the SK-MEL-28 melanoma cell line). Functionally, TTX-030 reverses adenosine-driven suppression of proliferation of activated $CD4^+$ and $CD8^+$ human T cells in a dose-dependent manner. Inhibition of CD39 by TTX-030 in CD3/CD28 stimulated peripheral blood mononuclear cells (PBMCs) in the presence of exogenous ATP increased proliferation of both $CD4^+$ and $CD8^+$ T cells from multiple donors. TTX-030 incubation with stimulated PBMCs led to increased secretion of pro-inflammatory cytokines interferon (IFN)-γ, interleukin (IL)-2, and tumor necrosis factor-α. Additionally, TTX-030 reversed adenosine-driven suppression of T cell IFN-γ responses in cytomegalovirus peptide recall assay.

2.2.2.3. Summary of Clinical Experience With TTX-030

As of Dec 2022, 2 Phase 1/1b clinical trials evaluating TTX-030 (Studies TTX-030-001 and -002) in subjects with solid-tumor malignancies were ongoing. Over 210 subjects have been treated with TTX-030 as monotherapy or in combination with anti-PD-1 agents with or without chemotherapy in the Phase 1 setting.

2.2.2.3.1. Overall

2.2.2.3.1.1. Pharmacokinetic Analysis

Clinical pharmacokinetic (PK) data are available from 2 ongoing studies. A summary of results from a pooled analysis of data from the 2 studies (3798 samples in 213 subjects) is available in the TTX-030 Investigator's Brochure.

[redacted]

2.2.2.3.1.2. Clinical Safety

TTX-030 monotherapy has shown favorable safety and tolerability in subjects with solid tumors in the first-in-human TTX-030-001 study. No dose-limiting toxicities (DLTs) were observed during monotherapy dose escalation in 21 subjects at dose levels ranging from 0.5 to 40 mg/kg every 3 weeks (Q3W) and the maximum tolerated dose was not reached. Based on the safety experience from monotherapy dose-escalation as well as PK modelling, the dose selected for expansion was 30 mg/kg Q3W or 20 mg/kg every 2 weeks (Q2W), with both infusion schedules preceded by a loading dose of 40 mg/kg. An additional 8 subjects received TTX-030

monotherapy (30 mg/kg Q3W, 40 mg/kg load) during the monotherapy dose expansion. Among the 29 subjects who received TTX-030 monotherapy, 11 subjects (37.9%) experienced Grade ≥3 adverse events (AEs) with only one attributed per investigator to TTX-030 (Grade 3 *generalized edema*).

In Studies TTX-030-001 and -002, the initial safety of TTX-030 as part of combination therapy was evaluated in the following cohorts:

- TTX-030 + pembrolizumab (Study TTX-030-001, Arm 2)
- TTX-030 + nab-paclitaxel + gemcitabine (Study TTX-030-001, Arm 4)
- TTX-030 + budigalimab + mFOLFOX6 (Study TTX-030-002, Cohort 1)
- TTX-030 + budigalimab + docetaxel (Study TTX-030-002, Cohort 2)

Evaluation of safety lead-in cohorts preceded subsequent enrollment. Across all 4 safety lead-ins, only 1 subject reported a DLT – with the combination of TTX-030 + budigalimab + docetaxel, Grade 3 *rash maculo-papular* and Grade 3 *pneumonitis* were reported on Study Day 92. Both events were considered related to budigalimab.

Overall, the safety profile of combinations evaluated in the Phase 1 setting was favorable, without a notable increase in frequency or severity of adverse events from chemotherapy or anti-PD-1 treatment alone, including combinations of TTX-030+chemotherapy (n=37), TTX-030+anti-PD-1 (n=63), or TTX-030+chemotherapy+anti-PD-1 (n=104). Of note, the frequency and severity of immune-related adverse events (irAEs) observed with TTX-030 combined with anti-PD-1 antibodies (with or without chemotherapy) did not appear higher than what might be expected with PD-1 checkpoint inhibition alone.

2.2.2.3.2. Subjects with PDAC

Study TTX-030-001 and TTX-030-002 included a total of 59 subjects with PDAC treated with TTX-030 in combination with gemcitabine/nab-paclitaxel with or without the anti-PD-1 antibody budigalimab.

2.2.2.3.2.1. Safety in Subjects with PDAC

Refer to the TTX-030 Investigator's Brochure for the most up to date safety information.

The most common treatment-emergent adverse events (TEAE ≥10%) that were attributed to TTX-030 by investigators were fatigue (18 subjects, 30.5%), decreased appetite (8 subjects, 13.6%), anaemia, diarrhoea, rash maculo-papular, (7 subjects, 11.9% each), neutrophil count decreased (6 subjects, 10.2%). Grade ≥3 related AEs reported in 2 or more subjects were neutrophil count decreased (4 subjects, 6.8%) and anaemia (2 subjects, 3.4%). Serious adverse events that were reported as related to treatment were asthenia, pulmonary embolism, rash maculo-papular, seizure (1 subject, 1.7% each). There was 1 AE resulting in death (septic shock, not related to TTX-030) and 1 AE (same event) leading to withdrawal of TTX-030 (septic shock).

Safety results from 31 subjects treated in 2 expansion cohorts (Arm 4 of Study TTX-030-001 and Cohort 11 of Study TTX-030-002) are available for the combination of TTX-030 + gemcitabine/nab-paclitaxel in locally advanced (LA)/mPDAC. The most common TEAEs (≥10%) that were attributed by the investigator to TTX-030 were fatigue (13 subjects, 41.9%), nausea (6 subjects, 19.4%), neutrophil count decreased, decreased appetite, and neutrophil count

decreased (5 subjects, 16.1% each) and anaemia (4 subjects, 12.9%). The only Grade ≥3 related AEs reported in more than 1 subject was neutrophil count decreased (4 subjects, 12.9%). Serious adverse events attributed by the investigator to TTX-030 included asthenia and pulmonary embolism (1 subject, 3.2% each).

Safety results from 28 subjects treated in expansion Cohort 9 of Study TTX-030-002 are available for the combination of TTX+030 + budigalimab + gemcitabine/nab-paclitaxel in LA/mPDAC. The most common TEAEs (≥10%) attributed by the investigator to TTX-030 were fatigue (5 subjects, 17.9%), diarrhoea (4 subjects, 14.3%), decreased appetite, anaemia, rash maculo-papular (3 subjects, 10.7% each). No Grade ≥3 AEs attributed to TTX-030 were reported in more than 1 subject. Serious adverse events attributed by the investigator to TTX-030 included rash maculo-papular and seizure (1 subject, 3.6% each).

2.2.2.3.2.2. Clinical Activity in Subjects with PDAC

In October 2022, interim efficacy results were evaluated for the pancreatic cohorts in both Study TTX-030-001 and Study TTX-030-002.

For TTX-030 + nab-paclitaxel + gemcitabine in first line treatment of subjects with LA/mPDAC, the combined median time [range] on study was 6.1 months or 185 [1−770] days. Among 30 efficacy-evaluable subjects, 9 subjects experienced partial response (PR) or better as best response (PR: n=6; complete response [CR]: n=3; objective response rate [ORR]=30%), 13 experienced stable disease (SD), and 8 had progressive disease (PD). The median progression-free survival (PFS; Response Evaluable Criteria in Solid Tumors version 1.1 [RECIST 1.1]) was 5.7 months (24.7 weeks; 95% confidence interval [CI]: 16.1-32.7 weeks) (Table 2).

For TTX+030 + budigalimab + nab-paclitaxel + gemcitabine as first line therapy for subjects with LA/mPDAC, the median time [range] on study was 5.6 months or 171 [10−424] days. Among 27 efficacy-evaluable subjects, 9 subjects experienced PR as best response (PR: n=9; CR: n=0; ORR=33.3%), 13 (48.1%) experienced SD, and 5 (18.5%) had PD. The median PFS (RECIST 1.1) was 7.5 months (32.6 weeks; 95% CI: 22.6-45.0 weeks) (Table 2).

2.2.2.3.2.3. Preliminary Biomarker Results in Phase 1 PDAC Subjects

Retrospective analysis of Phase 1b results from the 28 Oct 2022 data cut-off date identified greater treatment benefit (ORR and PFS) in a subject subpopulation defined by high tumor expression of HLA-DQ at baseline (HLA-DQ^{high}, analyzed by NanoString) when compared to the low tumor expression of HLA-DQ (HLA-DQ^{low}) subgroup (Table 2).

Of the subjects treated with TTX-030 + nab-paclitaxel + gemcitabine, twenty had baseline tumor samples that were evaluable for the determination of expression levels of HLA-DQ by NanoString. Using an empirical cutoff, 12 subjects were defined as HLA-DQ^{high}, and 8 were defined as HLA-DQ^{low}. The ORR and median PFS in the HLA DQ^{high} and HLA-DQ^{low} subgroups of subjects were 58% and 11.1 months (48.4 weeks; 95% CI: 14.7 weeks-not estimable [NE]), and 13% and 3.5 months (15.2 weeks; 95% CI: 4.1-32.6 weeks), respectively (Table 2).

Of the subjects treated with TTX-030 + budigalimab + gemcitabine + nab-paclitaxel, fifteen had baseline tumor samples that were evaluable for the determination of expression levels of HLA-DQ at baseline by NanoString. Using an empirical cutoff, 12 subjects were defined as HLA-DQ^{high}, and 3 were defined as HLA-DQ^{low}. The ORR and median PFS in the HLA DQ^{high}

and HLA DQ^{low} subgroups of subjects were 58% and 9.6 months (41.7 weeks; 95% CI: 9.0 weeks-NE), and 0% and 5.2 months (22.6 weeks; 95% CI: 1.4-24.0 weeks), respectively (Table 2).

Table 2: Objective Response Rate/Median Progression Free Survival by HLA-DQ Subgroup

		ORR/Median PFS (RECIST 1.1), weeks (months)			
Treatment	**Arm (A) / Cohort (C)**	**Efficacy Evaluable**	**HLA-DQ Subgroups**		
			All Known	**High**	**Low**
Gem/NP + TTX-030	001 A4 & 002 C11	[N=30] 30% (9/30) **24.7 (5.7)** (95% CI: 16.1–32.7)	[N=20] 40% (8/20) **28.8 (6.6)** (95% CI: 14.0–48.4)	[N=12] 58% (7/12) **48.4 (11.1)** (95% CI: 14.7–NE)	[N=8] 13% (1/8) **15.2 (3.5)** (95% CI: 4.1–32.6)
Gem/NP + TTX-030 + budigalimab	002 C9	N=27 33% (9/27) **32.6 (7.5)** (95% CI: 22.6–45.0)	[N=15] 47% (7/15) **30.6 (7.0)** (95% CI: 9.0–51.4)	[N=12] 58% (7/12) **41.7 (9.6)** (95% CI: 9.0–NE)	[N=3] 0% (0/3) **22.6 (5.2)** (95% CI: 1.4–24.0)
Gem/NP + TTX-030 ± budigalimab	001 A4 & 002 C11 & 002 C9	N=57 32% (18/57) **29.9 (6.9)** (95% CI: 22.1–33.6)	[N=35] 43% (15/35) **30.6 (7.0)** (95% CI: 16.3–41.7)	[N=24] 58% (14/24) **41.7 (9.6)** (95% CI: 22.4–51.4)	[N=11] 9% (1/11) **16.3 (3.8)** (95% CI: 4.1–25.0)

Gem=gemcitabine; NP=nab-paclitaxel; ORR=Objective response rate; PFS=progression-free survival; RECIST 1.1=Response Evaluation Criteria in Solid Tumors
Data cut-off date: 28 Oct 2022

Overall, the retrospective analysis of the preliminary Phase 1b efficacy data suggests high HLA-DQ expression predicts benefit from treatment with TTX-030 in combination with gemcitabine + nab-paclitaxel ± budigalimab. The pooled results from the HLA-DQ^{high} subgroup has a greater benefit in terms of ORR (58%) and median PFS (9.6 months) when compared to the HLA-DQ^{low} subgroup (9% ORR, median PFS 3.8 months) (Table 2); these results are also favorable with respect to historical results from subjects treated with gemcitabine/nab-paclitaxel alone (23% ORR, median PFS 5.5 months, ABRAXANE PI, 2020). These efficacy and safety results support evaluation of TTX-030 in combination with gemcitabine + nab-paclitaxel ± budigalimab directed to subjects with PDAC and high HLA-DQ expression.

2.2.3. Background on Budigalimab (ABBV-181)

Budigalimab is a humanized, recombinant, human IgG1 L234A L235A monoclonal antibody that binds to cell surface-expressed PD-1 and blocks the interaction of the receptor with its ligands, resulting in checkpoint blockade similar to nivolumab and pembrolizumab. Budigalimab has a high affinity for PD-1 and blocks the interaction of PD-1 with both programmed cell death ligand-1 (PD-L1) and programmed cell death ligand-2 with high potency in multiple assay formats. The affinity of budigalimab for soluble monomeric PD-1 by surface plasmon resonance is 3.3 nM, which compares favorably to the published affinity for nivolumab (3.06 nM). Inclusion

of budigalimab in cellular assays of antigen-driven activation results in enhanced activation of responding T cells as evidenced by increased cytokine secretion. Budigalimab demonstrated tumor growth inhibition in vivo using a human-cell adoptive transfer tumor growth inhibition model.

Refer to the Budigalimab Investigator's Brochure for more information.

2.2.3.1. Summary of Clinical Experience in Oncology Trials with Budigalimab

Refer to the Budigalimab Investigator's Brochure for the most up to date safety information.

Preliminary safety data are available for 143 subjects treated with budigalimab as monotherapy in Study M15-891 (N=140) and Study M19-228 (N=3); preliminary safety data are also available for 409 subjects treated in the budigalimab combination with other agents.

As of October 2022, the budigalimab clinical program comprises 13 Phase 1 studies evaluating budigalimab administration as monotherapy in 143 subjects, and as combination therapy with rovalpituzumab tesirine (Rova-T), venetoclax, ABT-165, ABBV-927, ABBV-368, SC-003, SC-006, and ABBV-151, in 409 subjects.

Preliminary safety data were available for 143 subjects administered budigalimab as monotherapy in Study M15-891 and Study M19-228. Adverse events were reported in 141 subjects (98.6%).

Preliminary safety data are also available for 409 subjects treated in the budigalimab combination with other agents:

- Budigalimab in combination with Rova-T in Study M15-891 (N=31)
- Budigalimab in combination with venetoclax in Study M15-891 (N=10)
- Budigalimab in combination with ABT-165 in Study M14-006 (N=7)
- Budigalimab in combination with ABT-165 and paclitaxel in Study M14-006 (N=14)
- Budigalimab in combination with ABBV-927 in Study M15-862 (N=59)
- Budigalimab in combination with ABBV-368 in Study M16-074 (N=55)
- Budigalimab in combination with SC-003 in Study SCRX003-001 (N=3)
- Budigalimab in combination with SC-006 in Study M16-312 (N=9)
- Budigalimab in combination with ABBV-151 in Study M19-345 (N=145)
- Budigalimab in combination with ABBV-927 and ABBV-368 in Study M19-037 (N=27)
- Budigalimab in combination with ABBV-927 and carboplatin in Study M19-037 (N=21)
- Budigalimab in combination with ABBV-927 and mRRX in Study M20-723 (N=19)
- Budigalimab in combination with ABBV-011 in Study M17-327 (N=5)
- Budigalimab in combination with ABBV-368 in Study M19-894 (N=4)

[redacted]

[redacted]

2.2.4. Rationale for Combining TTX-030, Budigalimab, nab-Paclitaxel and Gemcitabine

Chemotherapy, including the combination of nab-paclitaxel and gemcitabine, remains an accepted standard for front-line treatment of mPDAC. Accumulating evidence indicates that some traditional chemotherapeutic agents (including anthracyclines and platinum agents) contribute to the long-term successful elimination of cancer by triggering cancer immune responses (Garnett et al, 2008; Vacchelli et al, 2014). The possible mechanism by which dying or dead tumor cells can induce an anticancer immune response is through their immunogenic properties, which trigger specific signaling pathways. One such pathway is the adenosine axis, which is enhanced following chemotherapy through release of intracellular ATP from dying cells. Inhibition of CD39-mediated ATP hydrolysis by TTX-030 has the potential to enhance accumulation of proinflammatory ATP in the tumor microenvironment. Enhancing intratumoral ATP concentrations may activate purinergic receptors, such as P2X7, that result in activation of the inflammasome and have potential to promote ATP-mediated antitumor responses, in addition to reducing generation of immune suppressive adenosine. Consequently, there is potential for additive effects when combining CD39 inhibitors with chemotherapy.

While impressive and durable responses are observed in subsets of solid tumor patients treated with anti-PD1 agents, response rates are limited in most types of cancer when used as a single agent and for most patients, clinical benefit is lost with time. Results to date suggest that a combination strategy may be needed to benefit subjects with PDAC. Co-expression of PD-1 and CD39 is highly prevalent on tumor-infiltrating lymphocytes and marks exhausted effector T cell subsets in multiple tumor types (Canale et al, 2018; Trishula data on file in Report 18-006-TRL). The rationale for combining CD39 with an anti-PD-1 antibody is that CD39 inhibition and subsequent ATP accumulation and adenosine reduction in the tumor microenvironment may lead to immune activation and immune activation may be greater and/or more durable in combination with anti-PD-1 therapy. This combination strategy is supported by the in vivo data generated in using an anti-murine CD39 antibody B66 in multiple syngeneic tumor models. Combining anti-CD39 therapy with an anti-PD-1 antibody in an MC38 syngeneic colorectal tumor model resulted in a significant decrease in tumor growth compared with either the control or monotherapy. Anti-PD1 treatment of SM1WT1, which is generally refractory- to immunotherapies, including anti-PD-1, shows marked tumor growth inhibition when anti-PD-1 treatment is combined with an antibody capable of inhibiting enzymatic function of CD39, suggesting that the latter treatment sensitizes an otherwise refractory tumor to checkpoint

blockade. These findings are consistent with previously reported data in $CD39^{-/-}$ animals, suggesting that anti-PD-1 treatment of MCA205 resulted in more pronounced tumor growth inhibition and increased number of complete responders in $CD39^{-/-}$ mice compared with the same treatment in wild-type mice (Lapierre et al, 2016).

In the Trishula Phase 1/1b Study TTX-030-001, TTX-030 was administered in combination with pembrolizumab and with nab-paclitaxel and gemcitabine. In the Phase 1/1b study TTX-030-002, TTX-030 was administered in combination with anti-PD-1 antibody treatment (pembrolizumab and budigalimab) and in combination with chemotherapy (nab-paclitaxel and gemcitabine) with and without anti-PD-1 antibody treatment. TTX-030 combinations were tolerable with preliminary results suggest a meaningful treatment effect for subjects with tumors with high HLA-DQ expression as outlined in Section 2.2.2.3.2.3.

Together, these findings suggest that TTX-030 combined with chemotherapy with or without anti-PD-1 therapy bears further investigation of clinical benefit in PDAC.

2.2.5. Rationale for Combining Budigalimab and Nab-paclitaxel Plus Gemcitabine

PD-1 and chemotherapy combinations have been approved and/or used as SOC in several indications and have a well-characterized safety profile. The combination of budigalimab with gemcitabine, nab-paclitaxel and TTX-030 did not show potentiation of toxicity of the individual agents in combination in the Phase 1 setting. Multiple Phase 1 and 2 studies with gemcitabine and nab-paclitaxel combined with therapeutics directed to PD-1 or PD-L1 have shown reasonable tolerability. Enhancing intra-tumoral anti-tumor immune activation by inhibition of CD39 may further benefit from blockade of PD-1 to promote T cell activation.

2.3. Benefit-Risk Assessment

This section summarizes the benefit-risk profile for each of the drugs that will be evaluated in this study. Overall, based on available nonclinical and clinical data, as well as information from other agents in these drug classes, the benefit-risk profiles of budigalimab in combination with chemotherapy with or without TTX-030 are judged acceptable for this clinical study.

2.3.1. TTX-030 Risks and Benefits

Inhibition of CD39 by TTX-030 has resulted in limited toxicity to date, without significant potentiation of immune related adverse events in combination with anti-PD-1 treatment in the Phase 1 setting (Section 2.2.2.3). The AE profile from the combination of gemcitabine and nab-paclitaxel is not anticipated to overlap with the immune-related potential AEs from TTX-030 or budigalimab. Though the safety of the combinations planned for evaluation in this Phase 2 study have been favorable to date in the Phase 1 setting, it is possible that TTX-030 may potentiate some of the exiting toxicities of the other agents in the combination setting.

Several investigational agents targeting adenosine receptors and CD73 in the adenosine pathway have entered Phase 1 trials and may offer insights on potential risks and benefits of targeting the adenosine pathway. Publicly disclosed safety data have been summarized here and in more detail in the Investigator's Brochure.

Clinical data from an ongoing Phase 1 trial with CPI-444 (NCT02655822), an oral small-molecule inhibitor of the adenosine 2a receptor ($A_{2a}R$), suggest that inhibiting adenosine-mediated suppression can be achieved with a favorable safety profile

(Fong et al, 2020). Similarly, no SAEs were reported in a Phase 1b/II study in Parkinson's disease with the same compound (Pinna, 2014). In addition, AB928, a small-molecule inhibitor of $A_{2a}R/A_{2b}R$, is being evaluated in combination with other agents in breast or ovarian cancer (NCT03719326), gastroesophageal cancer (GEC) or colorectal cancer (CRC; NCT03720678), and solid tumors (NCT03629756). Preliminary data showed a favorable safety profile, with no Grade 4 or 5 AB928-related TEAEs reported to date across the studies (Powderly et al, 2019).

Antibodies targeting CD73 have also entered clinical development. The anti-CD73 antibody, MEDI9447 (oleclumab), was evaluated for safety, efficacy, and PK alone or in combination with the anti-PD-L1 antibody, durvalumab (IMFINZI PI, 2018), in advanced pancreatic cancer or CRC (NCT02503774). No treatment-related deaths or DLTs were reported, and no SAEs were reported in any of the oleclumab monotherapy dose-escalation cohorts. Overall, treatment with oleclumab alone or with durvalumab demonstrated a manageable safety profile as measured by low incidence of treatment-related discontinuation and SAEs (Overman et al, 2018).

Overall, clinical experience with TTX-030 and other investigational agents targeting the adenosine pathway continues to show favorable tolerability, including in combination with anti-PD-1 agents and with chemotherapy.

2.3.2. Budigalimab Risks and Benefits

Budigalimab, a PD-1 inhibitor, is being evaluated by AbbVie, either as monotherapy or combination therapy, in subjects with various tumor types. Although the full efficacy/benefit has not yet been determined for budigalimab at this early stage of development, preliminary clinical data from a Phase 1 clinical study (M15-891) show initial clinical activity (Powderly et al, 2018) and indicate a safety profile of budigalimab that is consistent with that identified with other anti-PD-1 agents, and no unique toxicities have been observed. See Section 2.2.3.2 for details of the preliminary clinical results (Italiano et al, 2019).

Other PD-1 immune checkpoint inhibitors such as nivolumab and pembrolizumab have shown clinically meaningful improvements in OS, PFS, and durable clinical responses with manageable toxicity profiles in multiple clinical trials (Phase 3 cancer studies of subjects with metastatic NSCLC, melanoma, and renal cell carcinoma; Anagnostou et al, 2015 and Phase 3 cancer studies of subjects with PDAC; Timmer et al. 2021). These agents can be associated with novel, immune-related toxicities, including colitis, hepatitis, rashes, neuropathies, and less common events such as Stevens-Johnson syndrome (SJS). These toxicities can potentially be serious, some causing long-term damage and rarely death; however, most are manageable when recognized and treated promptly. Guidance for management of treatment-emergent toxicity following exposure to budigalimab is provided in Appendix 2.

2.3.3. Nab-paclitaxel and Gemcitabine Risks and Benefits

The benefit-risk profile of the combination of nab-paclitaxel and gemcitabine is well established as the combination is an accepted treatment regimen for front-line metastatic PDAC.

Refer to regional prescribing information for additional details with regards to risks and benefits.

3. STUDY OBJECTIVES

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

4. STUDY DESIGN

4.1. Overall 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

Note: Doses and schedules are provided in Section 6.1.

The study schema is depicted in Section 1.2.

Interim Safety Evaluations:

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 3 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. Details will be provided in the DMC charter.

Table 3: Optimized Toxicity Stopping Boundaries

Number of Subjects Treated per Arm	Hold Enrollment if Number of Subjects with Toxicity Events Exceeds
6	2
30	11

Let p_{tox} denote the true toxicity rate, the above stopping rule is obtained by maximizing Pr(claim that the treatment is acceptable p_{tox}= 0.2), while controlling Pr(claim that the treatment is acceptable | p_{tox} = 0.4) = 0.199, based on the following Bayesian stopping rule: the treatment is deemed unacceptably toxic if

$$\Pr(p_{tox} \leq 0.4 \mid data) < \lambda \left(\frac{n}{N}\right)^{\alpha/3}$$

where, n is the interim sample size, N is the maximum sample size, and λ =0.62 and α =0 are design parameters optimized, assuming a vague prior Beta(0.4,0.6) for p_{tox} to make "go/no-go" decision. Note that the original publication of the design used the probablity cutoff $\lambda \left(\frac{n}{N}\right)^{\alpha}$, here the attenuation factor 3 is added (I.e., α/3) to obtain stricter interim stopping boundaries to enhance safety.

Below are the operating characteristics of the BOP2 design for toxicity monitoring (Table 4).

Table 4: Operating Characteristics of Toxicity Monitoring

Scenario	Toxicity Rate	Early Stopping (%)	Claim Acceptable (%)	Average Sample Size
1	0.4	68.98	19.92	28.4
2	0.3	33.14	64.17	43.9
3	0.2	10.37	89.60	54.5

Interim Futility Assessments:

Two interim analyses for futility are planned at n=90 and n=120 subjects enrolled with a minimum of 16 weeks of follow up as outlined in Section 10.4.

4.1.1. Biomarker Testing Plan

A minimum 60 subjects (n=20/arm) will be enrolled irrespective of tumor expression level of HLA-DQ. Prospective selection of subjects for tumor HLA-DQ^{high} status may be employed subsequently. To enable this potential prospective selection, Trishula plans to develop one or more test methods to be validated for use at College of American Pathologists (CAP)/Clinical Laboratory Improvement Amendments (CLIA) certified laboratories. To date, HLA-DQ expression has been analyzed using a NanoString gene set. The Sponsor is developing a polymerase chain reaction (PCR)-based assay for evaluation in parallel.

Prior to implementation of testing for prospective selection of subjects for enrollment, Trishula submitted a Study Risk Determination (SRD) in accordance with FDA guidelines.[1] FDA assessed the planned use of the investigational device for prospective patient enrollment as having a non-significant risk (15 March 2024).

If an appropriate assay cannot be validated for prospective use, or if an appropriate cut point cannot be selected, the Sponsor may elect to continue to enroll all-comers, and use the NanoString platform and/or appropriate alternative for retrospective correlative analysis of HLA-DQ gene expression with clinical outcomes.

See Section 10.3.5.1 for additional information.

4.2. Rationale for Study Design

Based on preliminary data from the ongoing Phase 1b studies (Study TTX-030-001 and Study TTX-030-002), TTX-030 has been combined with budigalimab and chemotherapy with no new safety signals beyond what would be expected with anti-PD-1 therapy or chemotherapy alone. The combination of gemcitabine and nab-paclitaxel with TTX-030 with and without budigalimab were previously evaluated in the Phase 1b studies with the retrospective biomarker analysis in HLA-DQ subpopulations showing higher ORR and prolonged median PFS in HLA-DQ^{high} subjects (Section 2.2.2.3). The proposed 3-arm design (TTX-030 ± budigalimab + gemcitabine + nab-paclitaxel vs gemcitabine + nab-paclitaxel) is appropriate to evaluate the contribution of components and preliminary efficacy of the combinations.

4.3. Justification for Dose

4.3.1. Rationale for TTX-030 Doses and Schedules

Based on monotherapy safety experience as well as PK modelling, the doses explored during the Phase 1b portion of the clinical development (i.e., in Studies TTX-030-001 and -002) were 30 mg/kg Q3W or 20 mg/kg Q2W, with both infusion schedules preceded by a loading dose of 40 mg/kg. These doses and schedules were established to match administration of chemotherapy regimens anticipated to be evaluated in combination with TTX-030 while achieving serum trough concentration levels >50 µg/mL.

In this Phase 2 study, the proposed dosing regimen of TTX-030 is a 40 mg/kg intravenous (IV) loading dose on Cycle (C)1 Day (D)1 followed by 20 mg/kg IV Q2W beginning on C1D15, in 28-day cycles.

The proposed TTX-030 dose/schedule is informed by the totality of available nonclinical and clinical data. This includes clinical PK, pharmacodynamic, safety, and anti-tumor activity of TTX-030 observed in Studies TTX-030-001 and TTX-030-002, combined with key findings from the nonclinical pharmacology, PK, and toxicology studies:

[1] FDA Guidance; Principles of Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product (FDA 2016) and Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors for Significant Risk and Nonsignificant Risk Medical Device Studies; (FDA 2006).

- A loading dose of 40 mg/kg was implemented in Phase 1/1b study to achieve serum concentration of >50 μg/mL in Cycle 1. The 50 μg/mL concentration was found to be effective in generating maximum immune response in nonclinical studies.
- One time loading dose of TTX-030 of 40 mg/kg prior to C1D1 with 20 mg/kg Q2W was demonstrated to be safe and tolerable when combined with nab-paclitaxel + gemcitabine with or without budigalimab (See Section 2.2.2.3).
- C1D1 40 mg/kg loading-dose is predicted to achieve the effective concentration target of >50 μg/mL in nearly all subjects in Cycle 1.
- Proposed TTX-030 dosing schedule enables achieving optimal target TTX-030 concentration while ensuring subjects with PDAC do not experience a delay in chemotherapy administration.

Refer to the TTX-030 Investigator's Brochure for more information.

4.3.2. Rationale for Budigalimab Dose and Schedule

The recommended Phase 2 dose (RP2D) for budigalimab is 3 mg/kg Q2W. This dose was converted to a fixed dose of 250 mg Q2W and corresponding alternate dosing regimens of 375 mg Q3W and 500 mg Q4W based on preliminary safety, PK, and pharmacodynamic data and employing population pharmacokinetic modeling and simulations. Budigalimab at 250 mg Q2W will be used in the study. Further information on budigalimab pharmacology can be found in the current budigalimab IB.

4.3.3. Rationale for Nab-paclitaxel Plus Gemcitabine Doses and Schedules

The doses of nab-paclitaxel and gemcitabine are based on those currently in use for standard clinical practice. For additional information, please reference the most appropriate regional prescribing information.

5. STUDY POPULATION

Prospective requests for approval of protocol deviations to enrollment criteria, also known as waivers or exemptions, are not allowed.

5.1. Subject Inclusion Criteria

Subjects are eligible to be included in the study only if all of the inclusion criteria apply.

1. Capable of giving signed informed consent as described in Section 11.3, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
2. Male or female subjects ≥18 years of age at the time of Screening. (For South Korea: >18 years of age at the time of Screening).
3. Histologically or cytologically confirmed diagnosis of metastatic PDAC.
4. No prior systemic treatment for metastatic disease. Prior neoadjuvant or adjuvant systemic chemotherapy is permitted in the absence of disease progression within 6 months following last dose of chemotherapy.
5. No prior treatment with therapeutics specifically targeted to enhancing or de-repressing anti-tumor immunity including but not limited to checkpoint inhibitors or agents targeting the adenosine pathway (CD39, CD73 or adenosine receptor inhibitors).
6. Evidence of measurable disease as assessed by the investigator per RECIST 1.1 (Appendix 3).
7. Appropriate for treatment with nab-paclitaxel and gemcitabine chemotherapy.
8. Availability of tumor tissue (obtained by biopsy during Screening, or archival if collected within 90 days prior to the first dose of study drug and in the absence of intervening therapy). Biopsy of the primary site of disease in the pancreas or intrathoracic biopsies should not be performed to obtain tumor tissue for the purpose of this study. Subjects with contraindications for a biopsy procedure and without acceptable archival tissue samples are not eligible (Section 8.8).
9. Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1.
10. Subject must weigh ≥35 kg.
11. Resolution of adverse events from any prior chemotherapy, immunotherapy, or prior systemic anticancer therapy, radiotherapy, or surgery to Grade 1 or baseline (except Grade 2 alopecia and Grade 2 sensory neuropathy).
12. Women of childbearing potential and all men must agree to use 2 highly effective methods of contraception through 6 months (180 days) after the last administration of any study treatment.

    Note: Highly effective contraception methods include total abstinence; female sterilization (tubal ligation, bilateral oophorectomy, and/or hysterectomy); male sterilization (at least 6 months prior to Screening); intrauterine device or intrauterine hormone-releasing system; oral, injected, or implanted hormonal contraception with only progestogen at least 30 days before first dose; AND barrier methods of contraception; oral, injectable,

transdermal, or intravaginal combined hormonal contraception with estrogen and progestogen at least 30 days before first dose (Prescribing information should be followed if different from the above).

13. Subjects with history of congestive heart failure must have cardiac echocardiogram (ECHO) or multigated acquisition (MUGA) scan indicating left ventricular ejection fraction ≥45% within 28days prior to the first dose of study treatment.
14. Required baseline laboratory tests:
    a. Hematology: absolute neutrophil count (ANC) ≥1.2 k/μL, platelets ≥100 k/μL, hemoglobin (Hgb) ≥9 g/dL
    b. Coagulation: prothrombin time (PT) and International Normalized Ratio (INR) ≤1.2 x upper limit of normal (ULN), except for subjects receiving anticoagulation; subjects must be on a stable dose of warfarin for 6 weeks prior to enrollment.
    c. Kidney: Creatinine clearance (CrCl) or estimated glomerular filtration rate (eGFR) ≥40 mL/min calculated by Cockcroft-Gault or CKD-EPI (Appendix 6)
    d. Liver: AST and ALT ≤2.5 x ULN (or ≤5 x ULN with hepatic metastases); total bilirubin ≤2 x ULN (or ≤3 x ULN with Gilbert's syndrome); serum albumin ≥3.0 g/dL

The following Inclusion Criterion is applicable once prospective selection has been implemented:

15. Fresh or archival tumor tissue with HLA-DQ^{high} status per central laboratory testing.

5.2. Subject Exclusion Criteria

Subjects are excluded from the study if any of the exclusion criteria apply.

1. History of clinically significant allergy or hypersensitivity to planned study treatment components or to any monoclonal antibody (defined as any Grade 3 reaction lasting ≥48 hours despite optimal therapy)
2. History of SJS, Toxic epidermal necrolysis (TEN), or drug reaction with eosinophilia and systemic symptoms (DRESS)
3. History of autoimmune disease including but not limited to rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, non-infectious pneumonitis, interstitial lung disease (ILD), requiring systemic treatment that required systemic steroids or immunosuppressive agents within the last 2 years. Subjects with findings consistent with active autoimmune disease on Screening evaluation (computed tomography [CT] showing pneumonitis or ILD, physical examination findings) are not eligible. NOTE: History of vitiligo, autoimmune thyroiditis, or mild psoriasis are allowed.
4. Any active disease requiring systemic treatment with either corticosteroids (>10 mg daily prednisone or equivalent) or other immunosuppressive medications within 14 days prior to Day 1 of treatment. (NOTE: Inhaled, intranasal, intra-articular and topical [including ocular] steroids are allowed. Adrenal replacement [i.e., physiologic replacement] doses >10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease).
5. History of primary immunodeficiency, bone marrow transplantation, chronic lymphocytic leukemia, solid organ transplantation, or previous clinical diagnosis of tuberculosis

6. Use of investigational agent within 14 days prior to the first dose of study drug
7. Evidence of active central nervous system (CNS) metastatic disease or carcinomatous meningitis
8. Known history of human immunodeficiency virus (HIV) or other chronic immunodeficiency
9. Women who are pregnant or breastfeeding
10. Subject has received live vaccine within 28 days prior to the first dose of study drug
11. The subject has had major surgery per the Investigator within 28 days prior to the first dose of study drug, and the surgical wound is not adequately healed. A diagnostic or research biopsy does not exclude subjects from enrollment. Placement of a vascular access device such as a Port-A-Cath is not considered major surgery.
12. Has uncontrolled intercurrent illness including, but not limited to:
    a. Uncontrolled diabetes
    b. New York Heart Association (NYHA) Class 3 or 4 congestive heart failure
    c. Unstable angina, arrhythmia, or myocardial infarction within 6 months prior to Screening
    d. Poorly controlled hypertension, defined as a blood pressure consistently above 160/90 mmHg despite optimal medical management
    e. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring repeated drainage more than once every 28 days. Indwelling drainage catheters (e.g., PleurX®) are allowed
    f. Active or chronic viral hepatitis B or C infection
    g. Uncontrolled thyroid disease
    h. Active infection requiring systemic therapy; subjects receiving ongoing systemic antibiotic, antiviral or antifungal therapy for maintenance should be discussed with the medical monitor prior to Screening and enrollment
13. History of any other malignancy within the past 3 years except for: curatively treated carcinoma in situ; localized nonmelanoma or early-stage melanoma skin cancer; Stage 1 uterine cancer or localized prostate cancer that is considered adequately treated by the Investigator. Subjects with hematologic malignancies and anticipated OS of >5 years may be considered for enrollment but should be discussed with the Medical Monitor prior to evaluation.

5.3. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled/dosed in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes date of Screening, informed consent, reason for screen failure (e.g., eligibility criteria), and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

6. INVESTIGATIONAL PRODUCT

Investigational medicinal product (IMP) or investigational product (IP) is defined as any investigational intervention(s), marketed product(s), or placebo intended to be administered to a study subject according to the study protocol. In this protocol, TTX-030 and budigalimab (ABBV-181) are considered IMPs.

A non-investigational medicinal product (NIMP) is a medicinal product which is not classed as an IMP in a trial but may be taken by subjects during the trial. In this protocol, nab-paclitaxel and gemcitabine are considered as NIMPs and will be supplied locally by the trial sites.

6.1. Investigational Medicinal Product Description and Administration

The IMPs and NIMPs to be administered in this study are summarized in Table 5 and Study Treatments are summarized in Table 6. All other supplies not indicated below will be provided locally by the trial site, subsidiary, or designee, depending on local country operational or regulatory requirements.

Table 5: Product Descriptions

Investigational Product Name	Dosage Formulation	Dosage Level/ Potency	Dose Frequency	ROA	Sourcing	Product Status
TTX-030	Aqueous solution	40 mg/kg at C1D1, then 20 mg/kg Q2W from C1D15	Q2W	IV infusion	Sponsor	Experimental (IMP)
Budigalimab (ABBV-181)	Powder for solution for infusion	250 mg	Q2W	IV infusion	Sponsor	Experimental (IMP)
Nab-paclitaxel	Lyophilized powder for reconstitution	125 mg/m^2	Days 1, 8, and 15 of each 28-day cycle	IV infusion	Source Locally	Approved cancer therapy (NIMP)
Gemcitabine	Lyophilized powder for reconstitution	1000 mg/m^2	Days 1, 8, and 15 of each 28-day cycle	IV infusion	Source Locally	Approved cancer therapy (NIMP)

C=Cycle; D=Day; IMP=investigational medicinal product; IV=intravenous; NIMP=non-investigational medicinal product; Q2W=every 2 weeks; ROA=route of administration; SOC=standard of care.

Table 6: Study Treatments by Arm

Study Treatment(s)	Arm	Route/Duration
TTX-030 + nab-paclitaxel + gemcitabine	1	IV at least 60 minutes for TTX-030; approved agents administered per SOC
TTX-030 + budigalimab + nab-paclitaxel + gemcitabine	2	IV at least 60 minutes for TTX-030 and budigalimab; approved agents administered per SOC
nab-paclitaxel + gemcitabine	3	Approved agents administered per SOC

IV=intravenous; SOC=standard of care.
Note: IMP treatments are administered in the order listed. For Arms 1 and 2, there is a minimum of 60 minute observation time between infusions for IMP.

TTX-030 is a clear, colorless liquid formulation containing 30 mg/mL of TTX-030 in 10 mM sodium citrate, 280 mM sucrose, 0.02% polysorbate 20, and 1.0 mM, L-methionine; pH 6.5. Budigalimab is a lyophilized drug product, containing budigalimab 100 mg/vial. Budigalimab will be reconstituted as described in the Study Pharmacy Manual.

Administration of investigational products on clinic days will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially life-threatening serious reactions. Refer to Section 8.3 for details regarding safety reporting for this study. Subjects should be monitored for a minimum of 60 minutes following completion of TTX-030 and/or budigalimab infusions.

Refer to the Study IMP Manual for additional information on each agent and its administration requirements.

6.2. Study Drug Preparation/Handling/Storage/Accountability

6.2.1. Preparation and Handling

Instructions for preparation and handling of investigational products are provided in the Study Pharmacy Manual.

6.2.2. Storage

The Investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all investigational products received and that any discrepancies are reported and resolved before use of the investigational product.

Only subjects enrolled in the study may receive investigational products, and only authorized site staff may supply or administer investigational products. All investigational products must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

6.2.3. Accountability

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the

conclusion of the trial. For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the Investigator is responsible for ensuring that a local discard/destruction procedure is documented.

6.2.4. Standard Policies

Trial site personnel will have access to a central electronic treatment allocation/randomization system Interactive Response Technology (IRT) system to allocate subjects, to assign treatment to subjects and to manage the distribution of clinical supplies. Each person accessing the IRT system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

6.3. Randomization

6.3.1. Treatment Assignment and Randomization

The study will randomize approximately 180 subjects (n=60/arm). A minimum of 60 subjects (n=20/arm) will be enrolled irrespective of tumor expression level of HLA-DQ. Prospective selection of subjects for tumor HLA-DQ^{high} status may be employed subsequently. Subjects will be randomized 1:1:1 to one of 3 non-blinded treatment arms (28-day cycle):

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

All treatment assignments of subjects will be done using an IRT upon enrollment confirmation by the Sponsor or designee. A separate instruction manual will be provided to each site.

Investigational product will be administered at the study visits summarized in the Schedule of Activities (Section 1.3). Any returning investigational product that has been supplied to subjects should not be re-dispensed to any subjects.

6.3.2. Stratification

Treatment allocation/randomization will be stratified according to the following factors:

1. ECOG (0 vs 1)
2. Presence of liver metastases (yes vs no)
3. Geographic region (non-EU vs EU)

6.4. Treatment Compliance

Investigational products will be administered by qualified site personnel and tracked using drug accountability records. No additional measures of compliance will be instituted.

6.5. Treatment Modifications

Based on the available characterization of the mechanism of action and toxicology data, TTX-030 may cause AEs similar to, but independent of, concurrent therapy, may exacerbate the frequency or severity, or may have non-overlapping toxicities. The anticipated important safety risks and recommendations for toxicity management are summarized in Section 6.5.1.1.

Safety risks associated with budigalimab, gemcitabine, and nab-paclitaxel and recommendations for managing these risks are described in Section 6.5.1.2 and Section 6.5.1.3.

6.5.1. Treatment Modifications for TTX-030 and Chemotherapy With or Without Budigalimab

The Investigator may attribute each AE to the combination or to each agent alone. Subjects may have dose modifications for any of the drugs in a combination and each drug should be considered independently for interruption, dose modification, or withdrawal. If a toxicity does not resolve or the criteria for resuming study drug are not met, the subject should be discontinued from the agent(s) to which the toxicity is attributed. Holding of 1 agent and not the other agent(s) is appropriate if, in the opinion of the Investigator, the toxicity is clearly related to 1 of the study drugs. Appropriate documentation is required regarding the drug to which the Investigator is attributing the AE. If, in the opinion of the Investigator, the toxicity is related to the combination of these agents, then all of these agents should be held.

Specific anticipated or potential toxicities associated with the administration of TTX-030 in combination chemotherapy (e.g., gemcitabine, nab-paclitaxel) with or without budigalimab, as well as the measures taken to avoid or minimize such toxicity in this study, are described in the following sections.

6.5.1.1. Management of Toxicities Associated With TTX-030

Based on available clinical safety data, TTX-030 exhibited a favorable safety profile as monotherapy or in combination settings. Expected serious adverse drug reactions for TTX-030 considered for regulatory reporting purposes include cytokine release syndrome (CRS) and maculo-papular rash.

CRS occurs when a large number of immune cells become activated and release inflammatory cytokines that cause systemic symptoms, most commonly fever, chills, rash, and hypotension but may include other cardiopulmonary or renal system dysfunction. CRS has the potential to be life-threatening and assessing severity through a consensus CRS grading system may benefit patient management (Lee et al, ASTCT 2018). In cases with hypotension, hypoxia, or other clinically significant systemic organ toxicity, escalation of care and administration of the anti-IL6 antibody tocilizumab and corticosteroids should be considered. Please reference consensus guidelines for management of CRS (Lee et al, ASTCT 2018, Santomasso et al, ASCO 2021, Roselló et al, ESMO 2017 or regional equivalent) and discuss the case promptly with the medical monitor if CRS is suspected.

Infusion-related reactions, which may occur with biologic products, may occur with TTX-030 (see Section 6.5.2 for management of infusion-related reactions).

There are currently no recommendations for dose reductions of TTX-030.

- For Grade 3 AEs considered related to TTX-030, TTX-030 should be held until improvement to Grade ≤1 or return to baseline.
  - When the toxicity has improved to Grade ≤1 or has returned to baseline, TTX-030 may be restarted (discuss with the Medical Monitor).
  - If a dose is held for >28 days, Investigator is to consult with the Medical Monitor before reinitiating treatment.
- For Grade 4-related AEs, dosing of TTX-030 may be discontinued permanently (discuss with the Medical Monitor if permanent discontinuation is considered).

6.5.1.2. Management of Toxicities Associated with Budigalimab

Preliminary clinical data from the ongoing Phase 1 clinical study (M15-891) indicate that the safety profile of budigalimab is consistent with that identified with other anti-PD-1 agents, and no unique toxicities have been observed. See Section 2.2.3.1 for details of the preliminary clinical results.

Treatment modifications of budigalimab, including dose interruptions, may be required in the event of treatment-related toxicity. Dose reductions are not permitted. Treatment modifications and toxicity management guidelines for budigalimab are provided in Appendix 2. All toxicities will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0. When in doubt, the Investigator should consult with the Medical Monitor.

6.5.1.3. Management of Toxicities Associated with Nab-paclitaxel and Gemcitabine

Interruptions, delays, or other changes in the schedule of dosing should be managed per Institutional standard of care for nab-paclitaxel and gemcitabine; intervals between doses should be no shorter than 1 week. Dosing modifications should be discussed with the Medical Monitor.

6.5.2. Infusion Interruptions and Dosing Delays for TTX-030 and Budigalimab

During the infusion, interruptions are allowed in response to treatment toxicity. Following an interruption, the infusion may be restarted based on stability of the drug. Infusion reactions associated with TTX-030 and budigalimab are managed according to the guidelines in Table 7.

Table 7: Recommended Infusion-Related Reaction Management Guidelines for TTX-030 and Budigalimab

NCI CTCAE Grade	Treatment	Premedication at Each Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the Investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	**Stop infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to IV fluids, antihistamines, NSAIDs, acetaminophen, and narcotics. Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the Investigator. If symptoms resolve within 1 hour of stopping investigational product infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 to 50 mL/hour). Otherwise, dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further investigational product administration.**	A subject may be premedicated up to 2 hours prior to infusion of TTX-030 with: • Diphenhydramine 50 mg orally (or equivalent dose of antihistamine) • Acetaminophen 500 to 1000 mg orally (or equivalent dose of antipyretic)
Grade 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids, antihistamines, NSAIDs, acetaminophen, narcotics, oxygen, pressors, corticosteroids, and epinephrine. Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the Investigator. Hospitalization may be indicated. **Grade 4: Subject is permanently discontinued from further investigational product administration.**	No subsequent dosing

IV=intravenous; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; NSAID=nonsteroidal anti-inflammatory drug.

6.6. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded with the following:

- Reason for use

- Dates of administration, including start and end dates
- Dosage information, including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.6.1. Permitted Therapy

On dosing days, subjects should be discharged from the clinic with directions on self-administration of medications as needed to ameliorate potential delayed reactions to study treatment infusion, such as fever, chills, and myalgia. Medications may include antipyretics and antihistamines. All concomitant medications, including self-administered medications, are to be recorded.

Supportive care treatments that are indicated for treatment of AEs should be given as medically required. Standard supportive medications may be used such as hematopoietic growth factors to treat neutropenia or thrombocytopenia in accordance with American Society for Clinical Oncology guidelines and per institutional guidelines.

Concomitant medications may be necessary in the event of an acute infusion reaction, cytokine release syndrome, or another AE.

Low-molecular-weight heparin and Factor Xa inhibitors are allowed.

6.6.2. Prohibited Therapy

Concomitant treatments or procedures with any of the following are not allowed while the subject is receiving study treatment, unless approved by the sponsor, or as otherwise described in the protocol:

- Chronic administration of steroids at supra-physiologic doses (>10mg prednisone) are not permitted. Extended courses of corticosteroid treatment for immune-related adverse events should be discussed with the medical monitor. Inhaled, intranasal, intraocular, topical, and intra-articular steroids are allowed. Transient steroid administration is allowed as anti-emetic or chemotherapy pre-conditioning per institutional guidelines.
  A temporary course (≤3 days) of corticosteroids (i.e., contrast allergy, chronic obstructive pulmonary disease) may be permitted, depending on the duration and dose, after discussion and agreement with the Medical Monitor.
- Any drug treatments or procedures directed toward the treatment of cancer, including immunotherapy, chemotherapy, and radiation therapy. NOTE: Palliative radiation may be allowed during the trial on a case-by-case basis and to be discussed with Medical Monitor.
- Any investigational product, including investigational symptomatic treatment or procedures for solid tumors and investigational treatment or procedures for noncancer indications.
- Live vaccine administration is prohibited during the study and for 6 weeks following the last dose of budigalimab administration.

After Cycle 1, palliative radiation therapy for painful bone or skin metastasis is allowed if the subject is otherwise stable but will require temporary study treatment interruption prior to initiation of radiation therapy and resuming after the subject has recovered from any radiation toxicity.

Any concomitant treatment or procedure required for the subject's welfare may be given by the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding the treatment or procedure are recorded.

For each subject, premedications for the purpose of preventing infusion reactions during IV administration of TTX-030 or budigalimab should be avoided prior to the first infusion of the study drug, unless discussed with the Medical Monitor. Premedications may be given prior to subsequent doses if a subject exhibits signs or symptoms of infusion reaction during the first infusion of the study drug as assessed by the Investigator.

7. SUBJECT WITHDRAWAL/DISCONTINUATION CRITERIA

7.1. End of Treatment

Enrolled/treated subjects may continue treatment for up to a maximum of 24 months or until disease progression, intolerable toxicity, or death, whichever occurs first. If a subject discontinues any of the combination agents due to intolerance, then treatment with the remaining combination components may continue.

Subjects must discontinue the investigational product(s) if any of the following criteria are met:

- Completion of 24 months of study treatment
- Disease progression per Section 8.1
- Unacceptable toxicity as described in Section 6.5
- Investigator decision
- Subject decision
- Use of another (non-protocol-specified) anticancer therapy
- Pregnancy (see Appendix 5)
- Noncompliance with trial treatment or procedure requirements
- Meets criteria for End of Study

Subjects have the right to voluntarily discontinue treatment at any time for any reason. Treatment may be stopped with any agent at the discretion of the Investigator if the risk outweighs the benefit of continuing. A subject may be discontinued from investigational product by the Investigator or Sponsor if continuing with investigational product is inappropriate, the study plan is violated, or for administrative (site or study termination) or other safety reasons.

The primary reason for investigational product discontinuation should be documented on the appropriate electronic case report form (eCRF) page.

7.2. Follow-up Phase

When criteria for end of treatment (EOT) per Section 7.1 is met, subjects should have an EOT assessment and continue follow-up assessments as outlined in the Schedule of Activities (Section 1.3). If a subject initiates a new anticancer treatment within 30 days after the last dose of trial treatment, the EOT visit should occur before the start of a new therapy.

After completing the EOT visit, subjects will enter the post-treatment Follow-up phase provided they have documented disease progression at the EOT visit. Subjects who withdraw from treatment for reasons other than documented disease progression are required to continue to undergo tumor assessments (every 8 weeks) until progressive disease per RECIST 1.1 is documented, non-study subsequent anticancer therapy is initiated, or criteria are met for End of Study (Section 7.3).

7.2.1. Follow-up After Disease Progression

Information on survival follow-up and subsequent anticancer treatment will be collected for all subjects via telephone calls every 12 weeks after the last dose of study treatment. The first follow-up visit should occur no sooner than 12 weeks after the last dose of study treatment. Follow-up visits for OS assessments for subjects not receiving tumor assessment can be conducted remotely over the phone.

7.3. End-of-Study

At completion of follow-up, subjects may discontinue the study for any of the following reasons. No additional data will be collected once a subject completes or withdraws from the study.

- Death
- Lost to follow-up
- Study termination by the Sponsor
- Withdrawal of Consent
  - If a subject requests to be withdrawn from the study, the request must be documented in the source documents and signed by the Investigator. The primary reason for withdrawal from the study should be documented on the appropriate eCRF page. If the subject withdraws from the study, the Sponsor may retain and continue to use any data collected before the withdrawal of consent and Study staff may use a public information source (e.g., county records) to obtain information about survival status only.

7.4. Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study or not.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study if the following parameters are met:
  - Site staff are unable to contact the subject within 30 days after the first missed scheduled visit, with 3 documented attempts at contact. Documentation must be filed in the subject's medical records.

7.5. Subject Replacement

A subject who discontinues from the trial will not be replaced.

7.6. Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. Enrollment for the purposes of this trial is defined by randomization. The overall trial ends when the last subject completes the last study-related phone call or visit, discontinues from the trial, or is lost to follow-up.

7.7. Early Trial Termination

The trial may be terminated early if safety and efficacy clinical endpoints are not met or the risk/benefit ratio to the trial population fails to obtain the expected benefit. In addition, further recruitment in the trial may be stopped due to the following reasons but not limited to insufficient compliance with the protocol, Good Clinical Practice (GCP) and/or other applicable regulatory requirements, or study procedure-related concerns.

8. STUDY ASSESSMENTS AND PROCEDURES

Please see Section 1.3 for the Schedule of Activities to be performed during the study. Subjects must start treatment within 28 days of signing the informed consent form.

All activities should be performed and documented for each subject in the order shown in the Schedule of Activities, if feasible. Subjects will be closely monitored for safety and tolerability throughout the study. Subjects should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable as deemed by the Investigator.

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other administrative disruption that precludes the visit, the visit should be scheduled on the nearest following feasible date.

Coronavirus disease 2019 (COVID-19) guidance from applicable local regulatory authorities will be followed as necessary during the study in order to ensure subject safety. Confirmed diagnosis will be collected as per Section 8.3. Variance from the study assessments schedule may be permitted at the Sponsor's discretion in consultation with the Investigator and will be documented accordingly.

Collection of any non-safety-related data or subject samples may be terminated by the Sponsor at any time if further collection of such data or samples is also not related to the study's primary or secondary objective. The decision to discontinue any data collection will be communicated to the sites and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by means of a memorandum and will not require a protocol amendment.

8.1. Efficacy Assessments

Subjects will undergo tumor assessments as designated in the Schedule of Activities (Section 1.3) until disease progression (regardless of whether the subject is still receiving treatment), starts subsequent anticancer treatment, or until the subject reaches end of study. CT scans with contrast of the chest, abdomen, and pelvis (or an acceptable alternative – see below) are required for all subjects and should be performed in accordance with RECIST 1.1 (Section 12.3).

Tumor assessments will include all known or suspected disease sites. If contrast is contraindicated (i.e., in subjects with known contrast dye allergy or impaired renal clearance), CT without contrast, magnetic resonance imaging (MRI), or positron emission tomography (PET) scans will be allowed. The imaging modality used, selected anatomic regions, target lesions, non-target lesions and locations 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.

Anatomic regions included in the baseline CT scans beyond chest, abdomen and pelvis should be per disease history and clinical symptoms and repeated for all post-treatment tumor assessments.

If a CT scan for a tumor assessment is performed in a PET-CT scanner, the CT acquisition must be consistent with the standards for a diagnostic CT scan with contrast.

Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. Results must be reviewed by the Investigator before dosing at the next cycle. All Screening and supplemental imaging must be submitted to the central imaging vendor.

8.1.1. Tumor Imaging at Screening

Measurable and evaluable lesions, as defined by tumor-specific response criteria (RECIST 1.1; Appendix 3), should be assessed and documented at Screening. Previously radiated lesion(s) should not be designated as a target lesion. Selected target lesions should not have received radiation therapy within 6 months prior to Screening. Response assessments performed as SOC prior to obtaining informed consent and within 28 days prior to enrollment do not have to be repeated at Screening if scan images meet protocol requirements.

8.1.2. Tumor Imaging Following Enrollment

On-study imaging assessments should be performed every 8 weeks. Imaging timing should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression per RECIST 1.1 (see Appendix 3) is documented, non-protocol-specified anticancer treatment is initiated, or criteria are met for End of Study (Section 7.3), whichever occurs first.

8.1.3 Post End-of-Treatment Imaging Follow-up and Overall Survival

Subjects who discontinue treatment for reasons other than documented disease progression will continue to undergo tumor assessments (~every 8 weeks) 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.

The first follow-up visit should occur no sooner than 12 weeks after the last dose of study treatment. Follow-up visits for OS assessments for subjects not receiving tumor assessment can be conducted remotely over the phone (See Section 7.2.1).

8.2. Safety Assessments

Safety assessments will consist of monitoring and recording of AEs, including SAEs, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study. The planned timing for all safety assessments is provided in the Schedule of Activities (Section 1.3).

Certain types of events require immediate reporting to the Sponsor, as described in Section 8.3.1.1.

8.2.1. Medical History, Prior Medications and Demographic Data

Medical history, including clinically significant diseases, surgeries, and cancer history will be recorded at Screening (Section 1.3).

In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the subject from 30 days prior to Screening through 30 days after the last dose of study treatment will be recorded.

Demographic data may include age, sex, and race/ethnicity as applicable per local regulatory requirements.

8.2.2. Physical Examinations

Physical examinations (complete and symptom-focused) will be performed as designated in the Schedule of Activities (Section 1.3). A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, GI, genitourinary, and neurological systems. Any abnormality identified at Screening should be recorded on the General Medical History and Conditions eCRF page.

For a symptom-focused examination, only the relevant or affected body system(s) must be examined and a complete physical examination is not required.

ECOG performance status (see Appendix 1) should be assessed per the Schedule of Activities (Section 1.3).

Changes from Screening abnormalities should be recorded in subject notes. New or worsened clinically significant abnormalities should be recorded as AEs in the Adverse Event eCRF page.

8.2.3. Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure (while the subject is in a seated or semi-recumbent position), and temperature (at baseline and then as clinically indicated). Vital signs should be measured at the specified timepoints outlined in the Schedule of Activities (Section 1.3).

Vital signs collected during the study (including those collected during an AE) will be captured in the eCRF. All vital signs collected per protocol should be documented in the subject's medical record.

8.2.4. Electrocardiograms

Triplicate 12-lead electrocardiogram (ECG) recordings approximately 2 minutes (or 1 minute, if applicable) apart will be obtained. Additional ECGs and/or other cardiac monitoring during subject's study participation may be performed as medically indicated as outlined in the Schedule of Activities (Section 1.3).

All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the Investigator must review, sign, and date all ECG tracings.

8.2.5. MUGA/ECHO

MUGA/ECHO is required for subjects with a history of congestive heart disease at Screening. Follow-up MUGA/ECHO assessment will be obtained during the study as per Investigator's discretion (Section 1.3).

8.2.6. Clinical Safety Laboratory Assessments

Blood samples for clinical safety laboratory testing (Table 8) will be collected at the timepoints described in the Schedule of Activities (Section 1.3).

Additional or repeated clinical laboratory testing may be performed while on treatment as clinically indicated by the Investigator. Laboratory assessments may be performed up to 3 days prior to treatment day of subsequent cycles as specified in Section 1.3. Extensive out of window (e.g., >1 week) visits are to be discussed with the Sponsor or designee. On treatment days, samples for clinical laboratory testing should be drawn prior to the infusion.

The Investigator or qualified designee must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be printed and available with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease unless judged by the Investigator to be more severe than expected for the subject's condition.

In the event of Grade 3 or Grade 4 laboratory toxicity, the test for the abnormal laboratory value should be repeated until the event is resolved to Grade ≤1 or baseline.

Table 8: Safety Laboratory Tests for Analysis

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood (qual)	Serum β-human chorionic gonadotropin (β-hCG) pregnancy test[a]
Hemoglobin	Alkaline phosphatase	Glucose (qual)	Prothrombin time (PT) (International Normalized Ration [INR])[e]
Platelet count	Alanine aminotransferase (ALT)	Protein (qual)	Partial thromboplastin time (PTT) or activated PTT (aPTT) [e]
White blood cell (WBC) (total and differential)	Aspartate aminotransferase (AST)	pH	Pituitary tests (Screening only): adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), growth hormone (GH)
Red blood cell count	Carbon dioxide (CO_2 or Bicarbonate) [b]	Specific gravity	Serology (Screening only): hepatitis B surface antigen (HbsAg), hepatitis B core antibody (anti-HBc), and hepatitis C virus antibody (anti-HCV)
Absolute neutrophil count	Calcium	Microscopic examination if abnormal results are noted	
lymphocyte (%)	Chloride	Urine pregnancy test[a]	
basophils (%)	Creatinine		Total triiodothyronine (T3)[f]
eosinophils (%)	Gamma-glutamyltransferase (GGT)		Free thyroxine (FT4)
monocytes (%)	Glucose		Thyroid stimulating hormone (TSH)
	Magnesium		Follicle Stimulating Hormone (FSH)[g]
	Phosphorus		
	Potassium		
	Sodium		
	Total bilirubin		
	Direct bilirubin if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood urea nitrogen		
	Urea[c]		
	Other Analytes[d]		
	Amylase		
	C-reactive protein		
	Lactate dehydrogenase (LDH)		
	Lipase		
	Uric acid		

a. Perform in women of childbearing potential only. A serum pregnancy test is required at Screening. For subsequent visits, a urine pregnancy test is preferred. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
b. If these tests are not done as part of the standard of care in your region, then these tests do not need to be performed.
c. Urea may be substituted if Blood urea nitrogen is not available.
d. Required only at the Baseline visit.
e. Coagulation factors (PT/INR and PTT or aPTT) should be tested as part of the Screening procedures for all subjects. Any subject receiving anticoagulant therapy should be monitored per standard of care throughout the trial.
f. Total T3 is preferred, if not available free T3 may be tested.
g. As needed, FSH to be performed at Screening/Baseline to confirm post-menopausal status.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

Investigators will seek information on AEs at each subject contact. AEs reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative) or noted by study personnel will be recorded in the subject's medical record and on the AE eCRF page.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, that are considered related to the investigational product or study procedures, or that caused the subject to discontinue the investigational product(s) (see Section 12.4 Appendix 4).

8.3.1. Time Period and Frequency for Collecting Adverse Events, Serious Adverse Events, and Other Reportable Safety Event Information

All AEs (e.g., including confirmed COVID-19 positive) and SAEs will be collected from the time the subject signs informed consent through 30 days after the last administration of study treatment, or until initiation of a new systemic anticancer therapy, whichever occurs first. SAEs that the Investigator deems related to study treatment should be reported at any time in accordance with Section 8.3.1.1. AE review should be performed at the first Follow-Up visit only and directed at those AE attributed to study treatment.

The method of recording, evaluating, and assessing causality of an AE and SAE and the procedures for completing SAE reports are provided in Appendix 4.

8.3.1.1. Events Requiring Expedited Reporting to the Sponsor

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The Investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the Investigator becomes aware of the event. The following is a list of events that the Investigator must report to the Sponsor within 24 hours of becoming aware of the event, regardless of relationship to the investigational product:

- All SAEs (defined in Appendix 4)
- New cancer
- Pregnancies (see Section 8.3.5 for details on reporting requirements)
- Adverse events of special interest (AESIs; defined in Section 8.3.7)
- Overdose of investigational product

8.3.2. Follow-up Event Reporting

The Investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis

- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All AEs and SAEs will be followed until resolution, stabilization, the event is otherwise explained, the subject is lost to follow-up (as defined in Section 7.3), or the subject withdraws consent. Every effort should be made to follow all SAEs considered to be related to the investigational product or trial-related procedures until a final outcome can be reported. Further information on follow-up procedures is provided in Appendix 4.

For SAEs and pregnancies, the Sponsor or a designee may follow-up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

If the Investigator learns of any SAE, including a death, at any time after the end of AE reporting period, and he/she considers the event to be reasonably related to the investigational product or study participation, the Investigator must promptly notify the Sponsor or its designee. These events should be reported to the Sponsor as outlined in Appendix 4.

8.3.3. Method of Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting AE information at all subject evaluation timepoints. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences. Examples of non-directive questions include "How have you felt since your last clinic visit?" and "Have you had any new or changed health problems since you were last here?"

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of subjects and the safety of an investigational product under clinical investigation are met (see Section 8.3.1.1). Investigators must also comply with local requirements for reporting SAEs to the IRB/IEC or other local health authorities.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an investigational product under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.

Expectedness will be assessed using the Investigator's Brochure(s) as reference documents. Reporting requirements will also be based on the Investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators, as necessary.

An Investigator who receives an Investigator Safety Report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

Details of all pregnancies in female subjects and, if indicated, female partners of male subjects will be collected after the start of investigational product, through 6 months (180 days) after the last dose of any study treatment. Female subjects, as well as female partners of male subjects, of childbearing potential will be instructed to immediately inform the Investigator if they become pregnant during the study or within 6 months (180 days) after the last dose of any study treatment. If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of becoming aware of the pregnancy and should follow the procedures outlined in Appendix 5. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

Pregnancy should not be recorded on the Adverse Event eCRF page. The Investigator should discontinue the investigational product and counsel the subject, discussing the risks of pregnancy and the possible effects on the fetus. Monitoring of the subject should continue until the conclusion of the pregnancy. Any SAEs associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF page. In addition, the Investigator will submit a Pregnancy Notification Form when updated information on the course and outcome of the pregnancy becomes available.

8.3.6. Disease-related Events and/or Disease-related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

Progression of the cancer under study, as judged by the Investigator, is not considered a reportable event.

All deaths will be recorded on the Death eCRF page.

8.3.7. 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.

8.3.8. Sponsor Contact Information

8.3.8.1. Emergency Medical Contacts

Sponsor Medical Monitor Contact Information:

Siddhartha Mitra, MD, PhD
Trishula Therapeutics, Inc.
2268 Westborough Boulevard, Suite 302 #263
South San Francisco, CA 94080
smitra@trishulatx.com

Alternate Medical Monitor contact information will be provided in the study manual.

8.4. Treatment of Overdose

The Investigator must immediately notify the Trishula-designated Pharmacovigilance Group of any occurrence of overdose with study intervention. Overdose is defined as any dose higher than the dose specified to be administered in accordance with the protocol.

All overdoses should be reported to the Sponsor within 24 hours on a Safety Notification Form. Any AEs resulting from the overdose should be recorded on the Adverse Event eCRF page. If the associated AE fulfills seriousness criteria, the event should also be reported to the Sponsor as an SAE following the guidance in Appendix 4 . Details of signs and symptoms, clinical management, and outcome should be reported, if applicable. Overdoses should also be captured as protocol deviations. The Principal Investigator will be notified by Trishula of respective deviations and has the obligation to report them to the IRB/IEC.

8.5. Pharmacokinetics

Blood samples will be obtained to measure the PK of TTX-030 and budigalimab in serum. The samples will be collected according to the Schedule of Activities (see Section 1.3). If feasible, PK samples should not be drawn from the same arm (or port) in which study drug(s) (including chemotherapy) is (are) administered. Serum concentrations for TTX-030 and budigalimab will be determined using a validated assay. Any additional analytes may be analyzed using nonvalidated methods. Serum samples collected may be used for future assay development or validation activities. Instructions related to PK sample collection, processing, storage, and shipment are described in the Laboratory Manual.

8.6. Antidrug Antibodies

Blood samples required for the detection of antidrug antibodies (ADAs) to TTX-030 or budigalimab in serum will be collected according to the Schedule of Activities (see Section 1.3) and will be determined using a validated assay. When possible, ADA blood samples will be collected from the opposite (contralateral) arm to the arm used for study drug administration. Any additional analytes may be analyzed using non-validated methods. Serum samples collected may be used for future assay development or validation activities.

Instructions related to ADA sample collection, processing, storage, and shipment are described in the Laboratory Manual.

8.7. Pharmacodynamics/Biomarkers

Based on blood and tissue samples collected, assessments may include but are not limited to pharmacodynamic biomarkers in peripheral blood and tumor tissue relating to mechanism of action, immune responses, and association with PK/safety and/or clinical response. Analytes may be analyzed using non-validated methods. Samples may be used for future assay development or validation activities.

Instructions related to pharmacodynamic biomarker sample collection, processing, storage, and shipment are described in the Laboratory Manual.

8.8. Tumor Tissue Collection

All subjects must consent to provide a formalin-fixed paraffin-embedded (FFPE) tumor tissue sample at Screening. Fresh or archival tumor tissue at Screening with sufficient tumor tissue is required for enrollment (i.e., submission of an FFPE block from which fifteen 4-5 micron slides can be cut or submission of a minimum of 10 FFPE unstained slides; see below for more details on submission of FFPE tumor tissue). Tumor tissue will be sent to a central laboratory and tested for HLA-DQ biomarker levels using an RT-qPCR investigational use only (IUO) assay (RxDx). Additional exploratory biomarker analyses may be performed as well.

For Screening purposes during the prospective enrollment phase, the result for each subject screened (i.e., "HLA-DQ^{high}" for eligible and "HLA-DQ^{low}" for ineligible based on HLA-DQ biomarker levels) will be sent to the sites to determine eligibility of subjects to enter the study. The diagnostic assay for HLA-DQ biomarkers is currently investigational. While it has been analytically validated, its performance in selecting patients who respond to TTX-030 therapy has not yet been established. In light of this test being relatively new, there is a chance of false positive results or false negative results.

An optional on-study biopsy to collect fresh tumor tissue from an appropriately accessible lesion at C2D1 may only be performed if deemed safe by the Investigator.

Biopsies should be performed only if deemed safe by the Investigator. 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. Thus, if a subject does not have sufficient archival tissue and the only sites of disease amenable for biopsy are intrathoracic and/or pancreatic, the subject will not be eligible for this study.

Fresh or archival tissue shall be obtained either by core biopsy, excisional biopsy, or other surgical specimen. (Note: Fine needle aspirate is not adequate for fresh and/or archival tissue samples). Archival FFPE tumor tissue may be submitted as a Screening biopsy sample if it was obtained within 90 days prior to the first dose and if the subject has not had any intervening treatment. The Screening tumor tissue sample shall be submitted to the central laboratory during the Screening period. If feasible, the on-treatment biopsy should be obtained from the same site as the Screening biopsy and should be submitted to the central laboratory as soon as feasible.

Submission of FFPE tumor tissue: blocks are preferred; please ensure sufficient sample volume to allow for cutting of minimum fifteen 4-5 micron thickness slides. When submitting unstained slides, a minimum of 10 slides is required. Slides should contain at least 3 x 3 mm viable tumor tissue on every slide, and for which sample, tumor comprises at least 5% of total tissue present. The

slides should be freshly cut and submitted to the central laboratory within 14 days from the slide sectioning date, otherwise a new specimen may be requested.

If the sample is determined to be non-evaluable by the testing laboratory, a new sample should be submitted if available. This may include additional cut slides that are outside of the 14-day window from the slide sectioning date.

Instructions related to the sample collection, processing, storage, and shipment of tumor samples are described in the Laboratory Manual.

8.9. Sample Collection

8.9.1. Sample Collection and Storage

This study will collect samples for biomarker assessments in all subjects (where not prohibited by local regulations). The following samples will be collected and stored in accordance with applicable law for long-term research purposes:

- Blood
- Tumor tissue

These samples may be sent to one or more laboratories, collaborators, or research partners of the Sponsor. They may be kept for up to 15 years after study completion. Samples will be anonymized after study completion.

8.9.1.1. Sample Testing

The samples may be used to explore and identify biomarkers that inform the scientific understanding of the disease and/or their therapeutic treatments. They may also be used to develop tests or assays, including diagnostic tests related to the investigational product(s) being tested in the main study. The samples may also be used for DNA analyses directed to the cancer, such as whole-genome sequencing and/or RNA sequencing, in the hopes of elucidating any relationship to clinical outcomes in response to the investigational product(s). In addition, biomarkers identified in other clinical studies may also be assessed in the biomarker samples collected from subjects enrolled in this study. The decision to perform other biomarker assessments may be based on the clinical outcome of this study and/or the signals observed in other clinical studies or other information available at that time. The information obtained from analyses is solely used to further characterize drug effects and does not have clinical diagnostic or therapeutic implications for the individual subject.

The data generated from this research are exploratory in nature and are not expected to provide clinically meaningful information. Any information obtained is not intended for inclusion in the medical record. This research will not change the care the subject receives in this study. Therefore, the Sponsor will not provide the investigator, subject, or anyone else (e.g., family members, study investigators, primary care physicians, insurers, or employers) with the results of this research, unless required by law.

8.9.1.2. Protection of Data Privacy

Samples are labeled (or “coded”) with a study-specific number that can be traced or linked back to the subject by the investigator or site staff. The Sponsor will be blinded as to the subject’s

identity. Coded samples do not carry personal identifiers (such as name or social security number).

The specimens and data generated from the specimens will be made available for inspection upon request by representatives of national or local health authorities and, if stored or sent to third parties, by the Sponsor and its representatives or agents.

8.9.2. Pharmacodynamic Biomarkers and Future Biomedical Research

Subjects in this clinical trial will be asked to consent to provide biological samples for future biomedical research. Such research is for biomarker testing and hypothesis testing to address emergent questions not described elsewhere in the protocol (as part of the main study). This research may include genetic and genomic analyses (DNA), gene expression profiling (RNA), immunophenotyping, proteomics, metabolomics (blood or tissue), and/or the measurement of other analytes.

8.9.2.1. Subject Consent and Withdrawal from Long-Term Sample Storage

Any subject who has provided informed consent to participate in the study may take part in the future biomedical research. Subjects who do not wish to participate in the optional future biomedical research part of the study may still participate in the main study. Subject participation in this research is voluntary, and refusal to participate will not indicate withdrawal from the study. Refusal to participate will involve no penalty or loss of benefits to which the subject would otherwise be entitled.

Any sample or derivatives (such as DNA, RNA, and protein) may be stored for up to 15 years after study completion to assist in any research related to TTX-030 or cancer, and for potential diagnostic development. Samples will be anonymized after study completion. Subjects who consent to participate in this optional research may withdraw consent to the use of these samples at any time prior to sample anonymization after study completion. Subjects must notify the Investigator, and the Investigator must complete the appropriate documentation to notify the Sponsor and maintain such documentation in the site's study records. The Sponsor will make reasonable efforts to destroy the retained samples so that they cannot be used for future research. However, any analyses in progress at the time of the request for withdrawal or already performed prior to the request being received by the Sponsor will be retained. No new testing will be initiated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the Investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's identity and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

8.10. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics will not be evaluated in this study.

9. TRIAL GOVERNANCE AND OVERSIGHT

9.1. Data Monitoring Committee

To supplement the routine trial monitoring outlined in this protocol, a Data Monitoring Committee (DMC) will monitor the interim data from this trial. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the trial in any other way (e.g., they cannot be trial investigators) and must have no competing interests that could affect their roles with respect to the trial.

The DMC will make recommendations to the Sponsor per the DMC Charter regarding steps to ensure both subject safety and the continued ethical integrity of the trial. Also, the DMC will review interim trial results, consider the overall risk and benefit to trial subjects (see Section 10.4) and recommend to the Sponsor if the trial should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the trial governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is reviewed and approved by the DMC. The DMC will monitor the trial at an appropriate frequency, as described in the detailed DMC charter. The DMC will also make recommendations to the Sponsor executive committee and/or protocol team regarding steps to ensure both subject safety and the continued ethical integrity of the trial.

A DMC recommendation will be communicated to the Sponsor as agreed to in the DMC Charter.

10. STATISTICS

10.1. Sample Size Determination

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).

10.2. Analysis Sets

The analysis sets are defined in Table 9.

Table 9: Populations for Analysis

Population	Description
Intent-to-Treat (ITT) Analysis Set	All subjects who are randomized
ITT Analysis Set – HLA-DQ^{high}	All randomized HLA-DQ^{high} subjects
Safety Analysis Set	All randomized subjects who received at least 1 dose of study treatment
PK Analysis Set	All subjects who receive at least 1 dose of study treatment and have PK data
Immunogenicity Analysis Set	All subjects who receive at least 1 dose of study treatment and have available ADA data
Biomarker/Pharmacodynamic Analysis Set	All subjects who receive at least 1 dose of study treatment and have available biomarker data

ADA=antidrug antibody; PK=pharmacokinetics.

10.3. Statistical Analyses

10.3.1. Safety Analyses

The safety analysis will be based on the Safety Analysis Set by treatment group, as defined in Table 9 The incidence of AEs, as well as changes from baseline in vital signs, clinical laboratory

parameters, physical examination findings, ECOG performance status, and ECGs, will be analyzed.

Summary statistics will be provided for TEAEs, SAEs, and TEAE severity/grade, and relationship to the investigational product(s). The number and percentage of subjects reporting TEAEs will be summarized overall and by the worst grade, system organ class, and preferred term. Similarly, the number and percentage of subjects reporting TEAEs considered related to the investigational product(s) will be summarized. A subject will be counted once using the highest grade and level of causality if 1 or more occurrences of the same system organ class/preferred term are reported. AEs will be graded according to the NCI CTCAE v5.0 and coded using the Medical Dictionary for Regulatory Activities.

10.3.2. Efficacy Analyses

The efficacy analysis will be based on the ITT Analysis Set and the ITT Analysis Set-HLA-DQ^{high}, as defined in Table 9. The primary analysis for PFS will be conducted when approximately 54 PFS events from the SOC arm (Arm 3) and 1 TTX-030 arm (Arm 1 or 2) in the HLA-DQ^{high} subjects. Additional analysis for the primary and secondary endpoints may be conducted.

The efficacy endpoints to be analyzed are listed and defined in Table 10.

Table 10: Efficacy Endpoints

Endpoint	Description
Objective response rate	Defined as the percentage of subjects who achieve best overall response (BOR) of either complete response (CR) or partial response (PR)
Duration of response	Defined as the time from first documentation of disease response (CR or PR) until first documentation of progression or death from any cause, whichever occurs first
Progression-free survival	Defined as the time from randomization until first documentation of progression or death from any cause, whichever occurs first
Overall survival	Defined as the time from randomization until death due to any cause

BOR=best overall response; CR=complete response; PR=partial response.

ORR will be presented with corresponding 2-sided 95% CI based on Clopper-Pearson method. The ORR difference between each TTX-030 arm and the SOC arm will be estimated along with the associated 95% CI. The distribution of the time-to-event endpoints (duration of response, PFS, and OS) will be summarized using the Kaplan-Meier method. The Cox proportional hazards model will be used to estimate the hazard ratio and its associated 95% CI.

10.3.3. Pharmacokinetic Analyses

The PK analysis will be based on the PK Analysis Set, as defined in Table 9. Serum concentrations of TTX-030 and budigalimab and PK parameter values will be tabulated for each subject, as appropriate. Summary statistics will be computed for each sampling time and each parameter, as appropriate.

10.3.4. Immunogenicity Analyses

The immunogenicity analysis will be based on the Immunogenicity Analysis Set, as defined in Table 9. Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of subjects who develop detectable anti-TTX-030 or anti-budigalimab antibodies. The immunogenicity titer will be reported for samples confirmed positive for the presence of anti-TTX-030 or anti-budigalimab antibodies.

10.3.5. Biomarker Analyses

Biomarker analyses will be based on the Biomarker Population, as defined in Table 9.

10.3.5.1. HLA-DQ

To assess the prevalence of HLA-DQ^{high} and characterize the biomarker-response relationship, HLA-DQ expression will be analyzed retrospectively by one or more methods in addition to the Nanostring platform used in the Phase 1 experience with TTX-030. The prevalence of HLA-DQ^{high} is estimated at 60% based on the threshold previously chosen from characterization of HLA-DQ expression from biopsy samples evaluated from Phase 1 subjects with first line (1L) mPDAC in the TTX-030-001 and TTX-030-002 clinical studies and from analysis of additional tumor samples from subjects with PDAC. Cumulative biomarker and clinical outcome results in 1L mPDAC, including results from subjects enrolled in this study during the unenriched enrollment phase, may be used to assess the biomarker-response relationship and re-evaluate the previously chosen threshold along with potential alternatives to optimally delineate HLA-DQ^{high} status.

If the selection of the appropriate cut point is not clear, a conservative threshold may be used for the potential prospective selection to ensure a broad distribution of tumor HLA-DQ expression for analysis of biomarker-response associations in the final analysis. Alternatively, the study may continue enrollment without prospective selection for tumor HLA-DQ^{high} status.

10.3.5.2. Exploratory Biomarkers

Baseline and changes from baseline in exploratory biomarker measures may be summarized. Possible association between changes in biomarker measures of interest and PK exposure may be explored. Possible association between biomarker measures of interest (baseline and change from baseline) and clinical outcomes (e.g., tumor response) may be explored to evaluate potential predictive markers.

10.4. Interim Analyses for Futility

Two interim analyses (IAs) for futility are planned at n=90 and n=120 total subjects enrolled (with a minimum of 2 scans follow up [~16 weeks]). Futility at each IA will be declared, if the posterior predictive probability of a no-go decision at the final analysis is ≥94% for both experimental arms, in 3 HLA-DQ-enriched subgroups (40%, 50%, and 60% upper expression level). As the horizon for data maturity precludes the use of PFS for determining futility, the interim analyses will be based on ORR. A decision rule at the final analysis will be made if posterior probabilities of the true difference of ORRs (p_t is ORR for one treatment arm, p_c is ORR for the control arm [for both treatment arms]) in all comparisons are:

$$PP(p_t - p_c > 0.1|D) < 0.65 \text{ and } PP(p_t - p_c > 0.2|D) < 0.1$$

Then results will be considered a no-go. The posterior probability will primarily be based on observed data from 40 HLA-DQ^{high} subjects in each arm and also use partial historical information (15% weight). The historical information assumes 57% and 33% response rates in treatment and control groups, respectively, in the enriched portion with a total weight (i.e., sample size) of n=21 in each group.

Based on the decision rule at the final analysis, simulations indicate that futility at each IA would be declared if ≥3 fewer responses occurred in the treatment arms than in the control arm.

Assuming that the 1st and the 2nd IAs are conducted at ~15 and ~20 HLA-DQ^{high} subjects enrolled per arm, respectively, and, in both cases, the true underlying control group rate is 30%, the chance of futility is about 23% when there is no true difference in the response rates in the treatment and control groups. When the true difference is 10% or 20%, the chance of futility drops to ~ 9% or ~2.5%, respectively.

11. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

11.1. Compliance with Laws and Regulations

This study will be conducted in full conformance with the International Council for Harmonisation (ICH) E6 guideline for Good Clinical Practice (GCP) and the consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, and applicable laws and regulations. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the US or under a US Investigational New Drug application will comply with US Food and Drug Administration regulations and applicable local, state, and federal laws. Studies conducted in regions other than the US will comply with the country and local laws, rules and regulations relating to the conduct of the clinical trial.

11.2. Institutional Review Board or Independent Ethics Committee

The protocol, protocol amendments, ICF(s), Investigator's Brochure, any information to be given to the subject, and relevant supporting information must be submitted to the IRB/IEC and reviewed and approved by the IRB/IEC before the study is initiated. In addition, any subject recruitment materials (e.g., advertisements) must be approved by the IRB/IEC.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by local IRB/IEC
- Promptly documenting and reporting any deviations that might have an impact on subject safety and data integrity to the Sponsor and to the IRB/IEC in accordance with established requirements, policies, and procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations, ICH guidelines, the IRB/IEC, and all other applicable local regulations.

11.3. Informed Consent

The Investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the

requirements of 21 Code of Federal Regulations 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign and date the ICF.

If applicable, the ICF will contain separate sections for any optional procedures. The Investigator or authorized designee will explain to each subject the objectives, methods, and potential risks associated with each optional procedure. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason without loss of benefits or medical care that would normally be provided. A separate, specific signature will be required to document a subject's agreement to participate in optional procedures. Subjects who decline to participate will not provide a separate signature.

Subjects must be re-consented to the most current version of the ICF(s) (or to a significant new information/findings addendum in accordance with applicable laws and IRB/IEC policy) during their participation in the study. The medical record should document the re-consent process and that written informed consent was obtained using the updated/revised ICF for continued participation in the study.

A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative. All signed and dated ICFs must remain in the subject's study file or in the site study file and must be available for verification by study monitors at any time.

The final revised IRB/IEC-approved ICFs must be provided to the Sponsor for the purpose of health authority submission.

Subjects who are rescreened are required to sign a new ICF.

The ICF may contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for exploratory research. Subjects who decline to participate in this optional research will not provide this separate signature.

11.4. Administrative Structure

This trial is sponsored and managed by Trishula and its designees. The Sponsor or its designee will provide clinical operations management and study monitoring.

Central facilities may be used for certain study assessments throughout the study (e.g., specified laboratory tests and biomarker and PK analyses). Accredited local laboratories will be used for routine safety monitoring; local laboratory ranges will be collected.

11.5. Data Protection

The Sponsor maintains confidentiality standards by assigning a unique study-specific number to each subject enrolled in the study. This means that subject names are not included in data sets that are transmitted to any Sponsor location.

Subject medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the subject or as permitted or required by law.

Medical information may be given to a subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, the Sponsor or its designee, and the IRB/IEC for each study site, as appropriate.

11.6. Source Documentation

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site. Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Source documents (paper or electronic) are those in which subject data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subject-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, subject files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hard copy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, the name of the person making the change, and date of the change.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained as described in Section 11.11.

11.7. Data Quality Assurance

All subject data relating to the study will be collected via electronic data capture (EDC) on an eCRF unless transmitted to the Sponsor or designee electronically (e.g., central laboratory data, biomarker data, and other biological sample data). Trial sites will be responsible for data entry into the EDC system and will receive training for appropriate eCRF completion. The Investigator

is responsible for verifying that data entries are accurate and correct by electronically signing and dating the eCRF.

The Investigator must maintain accurate documentation (source data, see Section 11.6) that supports the information entered in the eCRF. The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data. Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

At the end of the study, the Investigator will receive subject data for his/her site in a readable digital format that must be kept with the study records. Acknowledgment of receipt of the subject data is required.

11.8. Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). Investigators are responsible for providing information on financial interests during the course of the study, and for 1 year after completion of the study as requested to allow the Sponsor to submit accurate financial certification or disclosure statements to the appropriate health authorities. It is the Investigator's/Sub-Investigator's responsibility to comply with any such request.

The Investigator/Sub-Investigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The Investigator/Sub-Investigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

11.9. Compliance with Law, Audit and Debarment

By signing this protocol, the Investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (e.g., International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Investigator also agrees to allow monitoring, audits, IRB/IEC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The Investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state, and local laws, rules, and regulations; and, for each subject participating in the trial, provide all data, and, upon

completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor or its authorized representatives by the Investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The Investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The Investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

The Investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

11.10. Study and Site Closure

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Reasons for terminating the study or any portion of the study may include, but are not limited to, the following:

- Discontinuation of further investigational product development
- The incidence or severity of AEs in this or other studies indicates a potential hazard to subjects
- Subject enrollment is unsatisfactory

The Sponsor will notify the Investigator if the Sponsor decides to discontinue the study.

Reasons for the early closure of a study site by the Sponsor or Investigator may include, but are not limited to, the following:

- Poor protocol adherence
- Inaccurate or incomplete data recording
- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- No study activity (i.e., all subjects have completed the study and all obligations have been fulfilled)

11.11. Retention of Records

The Investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation

includes, but is not limited to, the protocol, source worksheets, eCRFs, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/IECs, consent forms, Investigators' curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the Investigator agrees that documentation must be retained by trial site for 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product or for the maximum period required by applicable regulations of relevant national or local health authorities. No records may be disposed of without the written approval of the Sponsor. The Sponsor will notify the Investigator when the records are no longer needed. Following notification from the Sponsor, the documents may be destroyed, subject to local regulations.

Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

11.12. Publication Policy and Protection of Trade Secrets

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to health care professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results.

The Investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating Investigator will be designated in accordance with Trishula's publication policy. Authorship will be based on overall scientific contribution and subject enrollment.

12. SUPPORTING DOCUMENTATION

12.1. Appendix 1: Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light 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

Source: Oken et al, 1982.

12.2. Appendix 2: Budigalimab Treatment Modification and Toxicity Management Guidelines

The following guidelines were developed from the American Society of Clinical Oncology (ASCO) immune-related adverse event (AE) management guidelines.

These guidelines are general recommendations for the clinical situations listed below. Investigators should consult their local practices as well as the European Society for Medical Oncology (ESMO), the National Comprehensive Cancer Network (NCCN), and the Society for Immunotherapy of Cancer (SITC) published guidelines for management of immune-related toxicity (including events not listed in this appendix) following treatment with immune checkpoint inhibitors.

Investigators should also review the recommendations for dose modifications (Section 6.5).

Additional details and guidance regarding toxicities that are not described in this appendix (e.g., musculoskeletal toxicity, hematologic toxicity, cardiovascular toxicity, and ocular toxicity) may be found in the ASCO, ESMO, NCCN, and SITC guidelines for diagnostic workup and management of immune-related AEs following treatment with immune checkpoint inhibitors.

Table 11 contains general guidance regarding evaluating and managing immune-related TEAEs following budigalimab (ABBV-181) treatment. Additionally, Investigators should consult the study's Medical Monitor. In general, corticosteroids should be initiated promptly for suspected irAEs and continued until an alternate etiology for a toxicity is determined or per the guidelines below. If an alternative non-immune related cause is identified, it should be treated accordingly, and budigalimab treatment can be re-started/continued as clinically appropriate following discussion with the study's Medical Monitor.

Table 11: General Guidance Regarding Management of Immune-Related Adverse Event Following Budigalimab Treatment

Grade of Toxicity* (NCI CTCAE v5.0)	Management	Follow-Up
Grade 1 Mild; asymptomatic or mild symptoms; clinical ordiagnostic observations only; intervention not indicated.	• Continue study drug(s).	Continue clinical monitoring. If worsens: Treat as Grade 2 or Grade 3 – 4.
Grade 2 Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**	• Delay or permanently discontinue Study drug(s) therapy per guidance in Protocol Section 6.5.1.2. • Consult appropriate specialty. • Treat symptoms per local guidance. • Consider methylprednisolone 0.5 – 1 mg/kg/day IV (or equivalent oral corticosteroid dose).	If improves to baseline: Resume routine monitoring Resume study drug(s) therapy per protocol when symptoms improve to Grade 1 or baseline following discussion with the medical monitor. If symptoms worsen: Treat as Grade 3 – 4.
Grade 3 – 4 Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.*** Grade 4: Life-threatening consequences; urgent intervention indicated.	• Delay or permanently discontinue study drug(s) therapy per guidance in Protocol Section 6.5.1.2. • Consult appropriate specialty. • Treat symptoms per local guidance. • Initiate methylprednisolone 1 –2 mg/kg/day IV (or equivalent). • Add prophylactic antibiotics for opportunistic infections as clinicallyindicated.	If returns to Grade 2: Taper steroids over at least 1 month. Resume study drug(s) therapy per protocol when symptoms improve to Grade 1 or baseline following discussion with the medical monitor. If no improvement: Re-consult with appropriate specialty and consider additional therapy per local guidelines.

ADL=activities of daily living; CTCAE=Common Terminology Criteria for Adverse Events; IV=intravenous; NCI=National Cancer Institute

Subjects on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) once sustained clinical improvement is observed. Lower bioavailability oforal corticosteroids should be taken into account when switching to equivalent doses of oral corticosteroids.

* Adapted from the NCI-CTCAE v.5.0 general guideline regarding grading of AEs.

** Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

*** Self-care ADL refer to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.

12.2.1. Management of Infusion-Related Reactions

For each subject, premedications for the purpose of preventing infusion reactions during intravenous (IV) budigalimab (ABBV-181) may be administered based on the investigator's standard practice.

Pre-medications such as acetaminophen/paracetamol, diphenhydramine, or H2-blockers (e.g., 50 mg diphenhydramine, 50 mg ranitidine, and 500 – 1000 mg acetaminophen) may be given prior to subsequent doses if a subject exhibits signs or symptoms of infusion reaction during the first administration of budigalimab. Consider reducing the rate of infusion upon re-initiation or subsequent infusions. The infusion rate can be increased as tolerated in subsequent cycles.

In the event of a suspected infusion-related reaction, the infusion should be stopped, close observation should be initiated, management should be initiated as described below in Table 12, and institutional standard support care should also be administered.

Table 12: Infusion-Related Reaction Adverse Event Management Algorithm

Events	Management	Follow-Up
Infusion reactions[a]	**Any Grade:** Stop infusion of study drug(s). Supportive care for subjects with any new signs or symptoms suggestive of an infusion reaction in the first 4 hours after the end of the infusion of study drug should be initiated as described below. **Grades 1 - 2:** Appropriate medical therapy should be administered, such as acetaminophen/paracetamol, diphenhydramine, H2-blockers, meperidine, albuterol, or steroids (or per Institutional standard of care). Consider reducing the rate of infusion upon re-initiation per Institutional standard of care. **Grade 3 during the first administration of budigalimab (ABBV-181):** Appropriate medical therapy should be administered, such as acetaminophen/paracetamol, diphenhydramine, H2-blockers, meperidine, albuterol, or steroids (or per Institutional standard of care). Consider reducing the rate of infusion upon re-initiation per institutional standard of care. **Grade ≥3 after the first administration of budigalimab (ABBV-181) or any Grade 4 event:** Permanently discontinue the study drug(s).[c] Appropriate medical therapy should be administered, such as acetaminophen/paracetamol, diphenhydramine, H2-blockers, meperidine, albuterol, or steroids (or per institutional standard of care).	**Any Grade:** Initiate close clinical monitoring.[b] Subject with any new signs or symptoms suggestive of an infusion reaction in the first 4 hours after the end of the infusion of study drug should undergo clinical monitoring for progression for an additional period of time as dictated by the subject's clinical status and/or the opinion of the investigator. **Grades 1 - 2:** Subsequent dosing: Premedication may be considered per institutional standard of care. The infusion rate can be increased as tolerated in subsequent cycles but no faster than 60 (± 10) minutes for budigalimab (ABBV-181). **Grade 3 during the first administration of budigalimab (ABBV-181):** Subsequent dosing: Premedication may be considered per institutional standard of care. The infusion rate can be increased as tolerated in subsequent cycles but no faster than 60 (± 10) minutes for budigalimab (ABBV-181).

a. In the event of a suspected hypersensitivity reaction or infusion reaction, a supplemental CRF (which captures relevant clinical signs and symptoms) should be completed by the site.

b. Consider additional supportive care measures: fluid resuscitation, oxygen supplementation, intensive care monitoring, and airway protection.

c. Subjects who had their first occurrence of a Grade > 3 infusion reaction in the absence of steroid prophylaxis that resolves within 6 hours do not meet discontinuation criteria from the study.

12.2.2. Gastrointestinal Adverse Event Management Algorithm

Rule out alternative non-immune-related causes; corticosteroids should be initiated promptly for suspected irAEs and continued until an alternate etiology for a toxicity is determined or per the guidelines below and in Table 13. If a non-immune-related cause is identified, treat accordingly, and continue budigalimab (ABBV-181) therapy as clinically appropriate. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Investigators should review the section on GI toxicities published (Brahmer et al, 2018; Haanen et al, 2017; NCCN guidelines, 2020; Puzanov et al, 2017) guidelines for additional guidance regarding diagnostic evaluation of diarrhea and diagnostic evaluation and management of other GI toxicities.

NOTE: Diagnostic evaluation of all Grade ≥2 Diarrhea should include:

- Work-up of blood (complete blood count, comprehensive metabolic panel, thyroid-stimulating hormone (TSH), erythrocyte sedimentation rate, C-reactive protein) and stool (culture, *Clostridium difficile*, parasite, cytomegalovirus or other viral etiology, ova, and parasite).
- Consider testing for lactoferrin (for subject stratification to determine who needs more urgent endoscopy) and calprotectin (to follow-up on disease activity).
- Laboratories (hepatitis serology and blood QuantiFERON for tuberculosis) to prepare subjects to start infliximab should be routinely done in subjects at high risk for those infections and appropriately selected subjects based on infectious disease expert's evaluation.
- Imaging (e.g., CT scan of abdomen and pelvis and GI endoscopy with biopsy) should be considered as there is evidence showing that the presence of ulceration in the colon can predict a corticosteroid-refractory course, which may require early infliximab.
- Consider repeating endoscopy for subjects who do not respond to immunosuppressive agents; repeating endoscopy for disease monitoring can be considered when clinically indicated and when planning to resume therapy.

For Grade 3 and 4 events:

- Consider repeating endoscopy for subjects who do not respond to immunosuppressive agents; repeating endoscopy for disease monitoring should only be considered when clinically indicated and when planning to resume budigalimab (ABBV-181).

Table 13: Gastrointestinal Adverse Event Management Algorithm

Grade of Diarrhea(NCI CTCAE v5.0)	Management	Follow-Up
Grade 1 Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline.	• Study drug(s) may be continued or held if clinically indicated. • Monitor for dehydration and recommend dietary changes. • Facilitate expedited phone contact with subject/caregiver. • Consider gastroenterology consult for prolonged Grade 1 cases.	Clinical monitoring every 1 – 2 days forworsening symptoms. Educate subject to report worsening symptoms immediately. If worsens: Treat as Grade 2, 3, or 4.
Grade 2 Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL.	• Hold study drug(s) until symptoms recover to Grade 1. • Clinical monitoring every 1 – 2 days for worsening symptoms. • Initiate immunosuppressant maintenance therapy (<10 mg prednisone equivalent dose) if clinically indicated. • Initiate supportive care (i.e., IV fluids, Imodium if infection has beenexcluded). • Initiate corticosteroids, unless diarrhea is transient, with initial dose of1 mg/kg/day prednisone or equivalent. • Consult gastroenterology for EGD/colonoscopy, endoscopy evaluation to stratify subjects for infliximab therapy and to determine safety of restarting study drug(s). • Consider early treatment with infliximab based on the endoscopic findings (NOTE: Infliximab should not be used in cases of perforation orsepsis). • Consider stool inflammatory markers (lactoferrin and calprotectin).	If improves to Grade 1: Consider restarting study drug(s) therapy per protocol following discussion with the medical monitor. Taper corticosteroids over at least 4 – 6 weeks before resuming treatment, may consider resuming study drug(s) while on low-dose corticosteroids after an evaluation of the risks and benefits. Consider prophylactic antibiotics for opportunistic infections. Consider repeat colonoscopy to monitor disease activity prior to re-starting study drug(s). If worsens or persists >3 - 5 days with steroids: Treat as Grade 3 – 4.

Grade of Diarrhea(NCI CTCAE v5.0)	Management	Follow-Up
Grade 3 Grade 3: Increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL. (Please note that the ASCO guidelines also include incontinence in the definition of Grade 3 colitis)	• Hold study drug(s), review guidance in Protocol Section 6.5 for Grade ≥3 AEs lasting >14 days. • Clinical monitoring every 1 – 2 days for worsening symptoms, consider IVfluids, admit subject to hospital as clinically indicated. • Initiate corticosteroids (initial dose of 1 - 2 mg/kg/day prednisone or IV equivalent). • If symptoms persist ≥3 – 5 days or recur after improvement, consideradministering IV corticosteroid (i.e., methylprednisolone 1.0 -2.0 mg/kg/day IV) or non-corticosteroid (e.g., infliximab, NOTE:Infliximab should not be used in cases of perforation or sepsis). • Consult gastroenterology, consider colonoscopy if subject has been on immunosuppression and may be at risk for opportunistic infections as an independent cause for diarrhea (i.e., cytomegalovirus colitis) and for those who are anti-TNF or corticosteroid refractory. • Consider adding prophylactic antibiotics for opportunistic infections.	If improves: Continue steroids until toxicity resolves to Grade 1 then taper over at least 1 month, consider adding prophylactic antibiotics for opportunistic infections. Consider restarting study drug(s) therapy per protocol following discussion with the medical monitor. Consider repeat colonoscopy to monitor disease activity prior to re-starting study drug(s). If worsens or persists >3 - 5 days or recurs after improvement: Treat as Grade 4.
Grade 4 Life-threatening consequences; urgent intervention indicated.	• Permanently discontinue study drug(s) (review guidance in Protocol Section 6.5). Admit subject to hospital. • Administer 1 – 2 mg/kg/day IV methylprednisolone or equivalent until symptoms improve to G1, and then taper over 4 - 6 weeks. • Consider early infliximab 5 – 10 mg/kg if symptoms refractory to corticosteroid within 2 – 3 days (NOTE: Infliximab should not be used incases of perforation or sepsis). • Consult gastroenterology, consider lower gastrointestinal endoscopy if symptoms are refractory despite treatment or if there is concern for new infections.	If improves: Continue steroids until toxicity resolves to Grade 1 then taper over at least 1 month, consider adding prophylactic antibiotics for opportunistic infections. If worsens or persists >3 – 5 days: Discuss with study medical monitor, consult additional specialties as clinically indicated.

CTCAE=Common Terminology Criteria for Adverse Events; EGD=esophagogastroduodenoscopy; NCI=National Cancer Institute; TNF=tumor necrosis factor

Subjects on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to equivalent doses of oral corticosteroids.

12.2.3. Renal Adverse Event Management Algorithm

Rule out alternative non-immune-related causes; corticosteroids should be initiated promptly for suspected irAEs and continued until an alternate etiology for a toxicity is determined or per the guidelines below and in Table 14. If a non-immune-related cause is identified, treat accordingly, and continue budigalimab (ABBV-181) therapy as clinically appropriate.

Investigators should review the section on renal toxicities in the ASCO, ESMO, NCCN, and SITC (Brahmer et al, 2018; Haanen et al, 2017; NCCN guidelines, 2020; Puzanov et al, 2017) guidelines for additional guidance regarding diagnostic evaluation of elevated creatinine and diagnostic evaluation and management of renal toxicities.

Please also review NCI CTCAE v.5.0 criteria definition and grading of "acute kidney injury" events versus the definition and grading of "creatinine increased" (the term "creatinine increased" was used to develop Table 14.

Table 14: Renal Adverse Event Management Algorithm

Grade of Creatinine Elevation (NCI CTCAE v5.0)	Management	Follow-Up
Grade 1 Creatinine >1 – 1.5 × baseline; > ULN – 1.5 × ULN	• Continue study drug(s) therapy, may hold study drug(s) as clinically indicated. • Monitor creatinine weekly.	If creatinine returns to baseline: Resume routine creatinine monitoring per protocol. If creatinine worsens: Treat as described below for Grade 2, 3, or elevations.
Grade 2 Creatinine >1.5 – 3.0 × baseline; >1.5 – 3.0 × ULN	• Delay study drug(s) therapy. • Monitor creatinine every 2 – 3 days. • Initiate methylprednisolone 0.5-1 mg/kg/day IV (or equivalent oral corticosteroid dose) and rule out non-inflammatory causes of creatinine elevation. • Consult nephrologist. • Consider renal biopsy.	If creatinine returns to Grade 1: Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume study drug(s) therapy and routine creatinine monitoring per protocol. If creatinine elevation persists >7 days or worsens: Treat as described below for Grade 3 or 4 elevations.
Grade 3 Creatinine >3.0 × baseline; >3.0 – 6.0 × ULN	• Delay study drug(s) therapy, review guidance in Protocol Section 6.5 for Grade ≥3 AEs. • Monitor creatinine every 2 – 3 days. • Initiate methylprednisolone 1-2 mg/kg/day IV (or equivalent). • Consult nephrologist. • Consider renal biopsy.	If creatinine returns to Grade 1: Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume study drug(s) therapy and routine creatinine monitoring per protocol. If creatinine elevation persists >7 days or worsens: Treat as described below for Grade 4 elevation (including permanent discontinuation of study drug(s) therapy).

Grade of Creatinine Elevation (NCI CTCAE v5.0)	Management	Follow-Up
Grade 4 Creatinine >6.0 × ULN	• Permanently discontinue study drug(s) per guidance in Protocol Section 6.5. • Monitor creatinine daily. • Initiate methylprednisolone 1-2 mg/kg/day IV (or equivalent). • Consult nephrologist. • Consider renal biopsy.	If creatinine returns to Grade 1: Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections.

AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; IV=intravenous; NCI=National Cancer Institute; ULN=upper limit of normal

Subjects on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to equivalent doses of oral corticosteroids.

12.2.4. Pulmonary Adverse Event Management Algorithm

Rule out alternative non-immune-related causes; corticosteroids should be initiated promptly for suspected irAEs and continued until an alternate etiology for a toxicity is determined or per the guidelines below and in Table 15. If a non-immune-related cause is identified, treat accordingly, and continue budigalimab therapy as clinically appropriate.

Diagnostic evaluation for any grade pneumonitis should include chest X-ray, CT, pulse oximetry for all Grades; if Grade ≥2, evaluations may include the following infectious work-up: nasal swab, sputum culture and sensitivity, blood culture and sensitivity, and urine culture and sensitivity. Consider early consultation with a pulmonologist.

Investigators should review the section on pulmonary toxicities in the ASCO, ESMO, NCCN and SITC guidelines for additional details on diagnostic evaluation of pneumonitis and diagnosis and management of other lung toxicity (Brahmer et al, 2018; Haanen et al, 2017; NCCN guidelines, 2020; Puzanov et al, 2017).

Table 15: Pulmonary Adverse Event Management Algorithm

Grade of Pneumonitis(NCI CTCAE v5.0)	Management	Follow-Up
Grade 1 Asymptomatic; clinical or diagnostic observations only; intervention not indicated (Please note that the ASCO guidelines also describe pneumonitis confined to 1 lobe of the lung or 25% of lung parenchyma in the definition of aGrade 1 event of pneumonitis).	• Hold study drug(s) therapy. • May offer 1 repeat CT in 3-4 weeks. • In subjects with baseline testing, may offer a repeat spirometry/diffusing capacity of the lungs for carbon monoxide in 3-4 weeks. • If no improvement, treat as Grade 2. • Monitor subjects weekly with history and physical examination and pulse oximetry; may also offer chest x-ray. • Consider pulmonology and infectious disease consultations.	May resume study drug(s) with radiographic evidence of improvement or resolution. If worsens: Treat as described below for Grade 2 or Grade 3-4 toxicity.
Grade 2 Symptomatic; medical intervention indicated; limiting instrumental ADL (Please note that the ASCO guidelines also describe pneumonitis involving more than 1 lobe of the lung or 25%-50% of lung parenchyma in the definition of a Grade 2 eventof pneumonitis).	• Delay study drug(s) until resolution to Grade 1 or less. • Initiate prednisone 1-2 mg/kg/day and taper by 5-10 mg/weekover 4-6 weeks. • Consider pulmonology consultation for bronchoscopy with BAL. • Consider empirical antibiotics. • Monitor every 3 days with history and physical examination, pulse oximetry, and chest x-ray.	May resume study drug(s) with radiographic evidence of improvement to Grade ≤1 or resolution. If no clinical improvement after 48-72 hours of prednisone, treat as Grade 3.

Grade of Pneumonitis(NCI CTCAE v5.0)	Management	Follow-Up
Grade 3 – 4 Grade 3: Severe symptoms; limiting self-care ADL; oxygen indicated (Please note that the ASCO guidelines also describe pneumonitis involving all lung lobes or > 50% of lung parenchyma in the definition of a Grade 3 event of pneumonitis). Grade 4: Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation).	• Permanently discontinue study drug(s) per guidance in Protocol Section 6.5. • Hospitalization for further management. • Initiate empirical antibiotics. • Initiate methylprednisolone 1 – 2 mg/kg/day IV. • If no improvement after 48 hours, may add infliximab 5 mg/kg or mycophenolate mofetil IV 1 g twice a day or IVIG for 5 days or cyclophosphamide. • Pulmonary and infectious disease consults. • Bronchoscopy with BAL ± transbronchial biopsy.	If improved to baseline: Taper corticosteroids over at least 6 weeks and continue antibiotics with input from pulmonology and infectious disease.

ADL=activities of daily living; ASCO=American Society of Clinical Oncology; BAL=bronchoalveolar lavage; CT=computed tomography; CTCAE=Common Terminology Criteria forAdverse Events; IV=intravenous; IVIG=intravenous immunoglobulins; NCI=National Cancer Institute

Subjects on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to equivalent doses of oral corticosteroids.

Additional considerations: 1. gastrointestinal and pneumocystis prophylaxis with proton pump inhibitor and Bactrim may be offered to subjects on prolonged corticosteroid use (>12 weeks) according to institutional guidelines, 2. consider calcium and vitamin D supplementation with prolonged corticosteroid use, 3. role of prophylactic fluconazole with prolonged corticosteroid use (> 12 weeks) remains unclear and investigator should proceed according to institutional guidelines, 4. bronchoscopy + biopsy; if clinical picture is consistent with pneumonitis, no need for biopsy.

12.2.5. Primary Hypothyroidism Adverse Event Management Algorithm

Rule out alternative non-immune-related causes. Consider imaging as clinically indicated.

Primary hypothyroidism AE management guidelines are provided in Table 16.

Investigators should review the section on endocrine toxicities in the ASCO, ESMO, NCCN, and SITC guidelines for additional details on diagnostic evaluation and management of hypothyroidism and other immune-related endocrine AEs (Brahmer et al, 2018; Haanen et al, 2017; NCCN guidelines, 2020; Puzanov et al, 2017).

Table 16: Primary Hypothyroidism Adverse Event Management Algorithm

Grade of Hypothyroidism (NCI CTCAE v5.0)	Management	Follow-Up
Grade 1 Asymptomatic; clinical or diagnostic observations only; intervention not indicated (Please note that the ASCO guidelines also describe TSH < 10 mIU/L inthe definition of a Grade 1 event of hypothyroidism).	• Continue study drug(s). • Close clinical follow-up and monitoring of TSHand free T4 (FT4).	If worsens: Treat as Grade 2 or Grade 3 – 4.
Grade 2 Symptomatic; thyroid replacement indicated; limiting instrumental ADL (Please note that the ASCO guidelines also describe TSH persistently > 10 mIU/L in the definition of a Grade 2 event of hypothyroidism).	• Hold study drug(s) until symptoms resolve to baseline. • Consider endocrine consultation. • Prescribe thyroid hormone supplementation in symptomatic subjects with any degree of TSH elevation or in asymptomatic subjects with TSH levels that persist >10 mIU/L (measured 4 weeks apart). • Monitor TSH every 6 – 8 weeks while titratinghormone replacement to normal TSH. • FT4 can be used in the short term (2 weeks) to ensure adequacy of therapy in those with frank hypothyroidism where the FT4 was initially low.	When symptoms resolve to baseline/subject is clinically stable: Re-start study drug(s). Monitor thyroid function every 4 weeks while on study drug(s) or as needed for symptoms to ensure appropriate replacement. Repeat thyroid function testing as indicated by symptoms once stable. If worsens: Treat as Grade 3 – 4.

Grade of Hypothyroidism (NCI CTCAE v5.0)	Management	Follow-Up
Grade 3 – 4 Grade 3: Severe symptoms; limiting self-care ADL; hospitalization indicated. Grade 4: Life-threatening consequences; urgent intervention indicated (Severe symptoms, medically significant or life threatening consequences, unable to perform ADL).	• Hold study drug(s) until symptoms resolve to baseline with appropriate supplementation, review guidance in Protocol Section 6.5, for Grade ≥3 AEs lasting >14 days. • Endocrine consultation. • May admit for IV therapy if signs of myxedema(bradycardia, hypothermia). • Thyroid supplementation and reassessment as in Grade 2.	When symptoms resolve to baseline/subject is clinically stable: Consider re-starting study drug(s) (after reviewing guidance in Protocol Section 6.6 for Grade ≥3 AEs lasting >7 – 14 days). Monitor thyroid function every 4 weeks while on study drug(s) or as needed for symptoms to ensure appropriate replacement. Repeat thyroid function testing as indicated by symptoms once stable. If worsens: Re-evaluate with endocrinology and appropriate specialties, discuss with study medical monitor.

ADL=activities of daily living; AE=adverse event; ASCO=American Society of Clinical Oncology; CTCAE=Common Terminology Criteria for Adverse Events; FT4=free thyroxine;IV=intravenous; NCI=National Cancer Institute; T4=thyroxine; TSH=thyroid-stimulating hormone

Additional Considerations:

- For subjects without risk factors, full replacement can be estimated with an ideal body weight–based dose of approximately 1.6 ug/kg/day.
- For elderly or fragile subjects with multiple comorbidities, consider titrating up with a fixed low dose, starting at 25 – 50 ug per day.
- Extreme elevations of TSH can be seen in the recovery phase of thyroiditis and can be watched in asymptomatic subjects to determine whether there is recovery to normal within 3 – 4 weeks.
- Under guidance of endocrinology, consider tapering hormone replacement and retesting in subjects with a history of thyroiditis (initial thyrotoxic phase).
- Adrenal dysfunction, if present, must always be replaced before thyroid hormone therapy is initiated.

12.2.6. Hyperthyroidism Adverse Event Management Algorithm

Rule out alternative non-immune related causes. Consider imaging as clinically indicated.

Hyperthyroidism AE management guidelines are provided in Table 17.

Investigators should review the section on endocrine toxicities in the ASCO, ESMO, NCCN, and SITC guidelines for additional details on diagnostic evaluation and management of hypothyroidism and other immune-related endocrine AEs (Brahmer et al, 2018; Haanen et al, 2017; NCCN guidelines, 2020; Puzanov et al, 2017).

Conduct close monitoring of thyroid function every 2 to 3 weeks after diagnosis to catch transition to hypothyroidism in subjects with thyroiditis and hyperthyroidism.

Table 17: Hyperthyroidism Adverse Event Management Algorithm

Grade of Hyperthyroidism (NCI CTCAE v5.0)	Management	Follow-Up
Grade 1 Asymptomatic; clinical or diagnostic observations only; intervention not indicated (asymptomatic or mild symptoms).	• Continue study drug(s) with close clinical follow-up and monitoring ofTSH and FT4 every 2 – 3 weeks until it is clear whether there will be persistent hyperthyroidism or hypothyroidism.	If worsens: Treat as Grade 2 or Grade 3 – 4.
Grade 2 Symptomatic; thyroid suppression therapy indicated; limiting instrumental ADL.	• Consider holding study drug(s) until symptoms return to baseline. • Repeat TSH, FT4 every 2 – 3 weeks. • Consider endocrine consultation. • Consider beta-blocker (e.g., atenolol, propranolol) for symptomatic relief (review co-morbidities prior to starting beta-blocker). • Hydration and supportive care. • Corticosteroids are not usually required to shorten duration. • For persistent hyperthyroidism (>6 weeks) or clinical suspicion, consult endocrinology, work-up for Graves' disease (thyroid-stimulating immunoglobulin or TSH receptor antibody) and consider thionamide (methimazole or propylthiouracil), refer to endocrinology for Graves' disease.	When symptoms resolve to baseline/subject is clinically stable: Re-start study drug(s). Monitor thyroid function every 4 weeks while on study drug(s) or as needed for symptoms to ensure appropriate replacement. Repeat thyroid function testing as indicated by symptoms once stable. If worsens: Treat as Grade 3 – 4.

Grade of Hyperthyroidism (NCI CTCAE v5.0)	Management	Follow-Up
Grade 3 – 4 Grade 3: Severe symptoms; limiting selfcare ADL; hospitalization indicated. Grade 4: Life-threatening consequences; urgent intervention indicated.	• Hold study drug(s) until symptoms resolve to baseline with appropriate therapy, review guidance in Protocol Section 6.5 for Grade ≥3 AEs lasting >7 – 14 days. • Endocrine consultation. • Consider beta-blocker (e.g., atenolol, propranolol) for symptomatic relief (review co-morbidities prior to starting beta-blocker). • For severe symptoms or concern for thyroid storm, hospitalize subject and initiate prednisone 1 – 2 mg/kg/day or equivalent IV dose tapered over 1 – 2 weeks. • Consider also use of potassium iodide or thionamide (methimazole or propylthiouracil), with appropriate clinical monitoring.	When symptoms resolve to baseline/subject is clinically stable: Consider re-starting study drug(s) (after reviewing guidance in Protocol Section 6.6 for Grade ≥3 AEs lasting >7–14 days). Monitor thyroid function every 4 weeks while on study drug(s) or as needed for symptoms to ensure appropriate replacement. Repeat thyroid function testing as indicated by symptoms once stable. If worsens: Re-evaluate with endocrinology and appropriate specialties, discuss with study medical monitor.

ADL=activities of daily living; AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; FT4=free thyroxine; IV=intravenous; NCI=National Cancer Institute;TSH=thyroid-stimulating hormone

Additional Considerations:

- Thyroiditis is transient and resolves in a couple of weeks to primary hypothyroidism or normal. Hypothyroidism can be treated as above.
- Graves' disease is generally persistent and is due to increased thyroid hormone production that can be treated with antithyroid medical therapy.
- Physical examination findings of ophthalmopathy or thyroid bruit are diagnostic of Graves and should prompt early endocrine referral.

12.2.7. Primary Adrenal Insufficiency Adverse Event Management Algorithm

Rule out alternative non-immune related causes. Consider imaging as clinically indicated.

Conduct diagnostic work-up if adrenal insufficiency is suspected: adrenocorticotropic hormone (ACTH; morning), cortisol level (morning), and metabolic panel (sodium, potassium, bicarbonate/CO_2, glucose); consider ACTH stimulation test for indeterminate results.

If primary adrenal insufficiency (high ACTH, low cortisol) is found biochemically, evaluate for precipitating cause of crisis such as infection; perform an adrenal CT for metastasis/hemorrhage.

Primary adrenal insufficiency AE management guidelines are provided in Table 18.

Investigators should review the section on endocrine toxicities in the ASCO, ESMO, NCCN, and SITC guidelines for additional details on diagnostic evaluation and management of primary adrenal insufficiency and other immune-related endocrine AEs (Brahmer et al, 2018; Haanen et al, 2017; NCCN guidelines, 2020; Puzanov et al, 2017).

Table 18: Primary Adrenal Insufficiency Adverse Event Management Algorithm

Grade of Adrenal Insufficiency (NCICTCAE v5.0)	Management	Follow-Up
Grade 1 Asymptomatic; clinical or diagnosticobservations only; intervention not indicated (asymptomatic or mild symptoms).	• Consider holding study drug(s) until subject is stabilizedon replacement hormone. • Endocrine consultation. Replacement therapy with prednisone (5-10 mg daily) or hydrocortisone (10 - 20 mg orally every morning, 5-10 mg orally in early afternoon). • May require fludrocortisone (0.1 mg/day) for mineralocorticoid replacement in primary adrenal insufficiency. • Titrate dose up or down as symptoms dictate.	<u>If worsens:</u> Treat as Grade 2 or Grade 3 – 4. <u>When symptoms resolve to baseline/subject is clinically stable:</u> Re-start study drug(s). Monitor labs and clinically with endocrinologyguidance.
Grade 2 Moderate symptoms; medical intervention indicated.	• Consider holding study drug(s) until subject is stabilizedon replacement hormone. • Endocrine consultation. • Initiate outpatient treatment at 2 to 3 times maintenance(if prednisone, 20 mg daily; if hydrocortisone, 20-30 mg in the morning, and 10 - 20 mg in the afternoon) to manage acute symptoms. • Taper stress-dose corticosteroids down to maintenance doses over 5 - 10 days. • Maintenance therapy as in Grade 1.	<u>If worsens:</u> Treat as Grade 3 – 4. <u>When symptoms resolve to baseline/subject is clinically stable:</u> Re-start study drug(s). Monitor labs and clinically with endocrinologyguidance.

Grade of Adrenal Insufficiency (NCICTCAE v5.0)	Management	Follow-Up
Grade 3 – 4 Grade 3: Severe symptoms; hospitalization indicated. Grade 4: Life-threatening consequences; urgent intervention indicated.	• Hold study drug(s) until subject is stabilized on replacement hormone, review guidance in Protocol Section 6.5 for Grade ≥3 AEs lasting >14 days. • Endocrine consultation. • Hospitalize subject. • Initiate normal saline (at least 2 L) and IV stress-dose corticosteroids (hydrocortisone 100 mg or dexamethasone 4 mg [if the diagnosis is not clear and stimulation testing will be needed]). • Taper stress-dose corticosteroids down to maintenance doses over 7 - 14 days after discharge. • Maintenance therapy as in Grade 1.	If worsens: Re-evaluate with endocrinologist and other appropriate specialties. Consider imaging. When symptoms resolve to baseline/subject is clinically stable: Consider re-starting study drug(s) (after reviewing guidance in Protocol Section 6.6 for Grade ≥3 AEs lasting >7-14 days). Monitor laboratory parameters and clinically with endocrinology guidance.

ACTH=adrenocorticotropic hormone; AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; INV=intravenous; NCI=National Cancer InstituteAdditional Considerations:

- Primary and secondary adrenal insufficiency can be distinguished by the relationship between ACTH and cortisol. If the ACTH is low with low cortisol, then management isas per pituitary – hypophysitis guidance.
- Subjects on corticosteroids for management of other conditions will have low morning cortisol as a result of iatrogenic, secondary adrenal insufficiency. ACTH will also below in these subjects. A diagnosis of adrenal insufficiency is challenging to make in these situations (see pituitary-hypophysitis guidance).
- Emergent therapy for someone with suspected adrenal insufficiency is best done with dexamethasone as a stimulation test can still be performed. If the diagnosis is already confirmed, can use hydrocortisone 100 mg.
- All subjects need education on stress dosing and a medical alert bracelet for adrenal insufficiency to trigger stress-dose corticosteroids by emergency medical services.
- Endocrine consultation prior to surgery or any procedure for stress-dose planning.

12.2.8. Pituitary Hypophysitis Adverse Event Management Algorithm

Rule out alternative non-immune related causes.

Consider diagnosis with the following lab changes:

- Low ACTH with a low cortisol
- Low or normal TSH with a low FT4
- Hypernatremia and volume depletion with diabetes insipidus
- Low testosterone or estradiol with low luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

Diagnostic testing: Evaluate ACTH, cortisol (morning), TSH, FT4, and electrolytes. Consider evaluating LH, FSH, and testosterone levels in males or estrogen in premenopausal females with fatigue, loss of libido, and mood changes.

Consider MRI of the brain with or without contrast with pituitary/sellar cuts in subjects with multiple endocrine abnormalities with or without new severe headaches or complaints of vision changes.

Pituitary hypophysitis AE management guidelines are provided in Table 19.

Investigators should review the section on endocrine toxicities in the ASCO, ESMO, NCCN, and SITC guidelines for additional details on diagnostic evaluation and management of hypophysitis and other immune-related endocrine AEs (Brahmer et al, 2018; Haanen et al, 2017; NCCN guidelines, 2020; Puzanov et al, 2017).

Table 19: Pituitary Hypophysitis Adverse Event Management Guidelines

Grade of Hypophysitis(NCI CTCAE v5.0)	Management	Follow-Up
Grade 1 Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.	• Considering holding study drug(s) until subject is stabilizedon replacement hormones. • Hormonal supplementation as needed, using dosing as above for primary hypothyroidism and adrenal insufficiency (e.g., hydrocortisone 10 – 20 mg orally in the morning, 5 – 10 mg orally in early afternoon; levothyroxine by weight). • Testosterone or estrogen therapy as needed in those without contraindications. • Endocrine consultation. • Always start corticosteroids several days before thyroid hormone to prevent precipitating adrenal crisis. • Follow FT4 for thyroid hormone replacement titration (TSHis not accurate).	If worsens: Treat as Grade 2 or Grade 3 – 4. When symptoms resolve to baseline/subject is clinically stable: Re-start study drug(s). Monitor laboratory parameters and clinically with endocrinology guidance.
Grade 2 Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.	• Consider holding study drug(s) until subject is stabilized on replacement hormones. • Endocrine consultation. • Hormonal supplementation per Grade 1.	If worsens: Treat as Grade 3 – 4. When symptoms resolve to baseline/subject is clinically stable: Re-start study drug(s). Monitor laboratory parameters and clinically with endocrinology guidance.

Grade of Hypophysitis(NCI CTCAE v5.0)	Management	Follow-Up
Grade 3 - 4 Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care ADL. Grade 4: Life-threatening consequences; urgent intervention indicated.	• Hold study drug(s) until subject is stabilized on replacement hormones, review guidance in Protocol Section 6.5 for Grade ≥3 AEs lasting > 14 days. • Endocrine consultation. • Hormonal supplementation as in Grade 1. • Consider initial pulse dose therapy with prednisone 1 –2 mg/kg oral daily (or equivalent) tapered over at least 1 –2 weeks.	If worsens: Re-evaluate with endocrinologist and other appropriate specialties. Consider imaging. When symptoms resolve to baseline/subject is clinically stable: Consider re-starting study drug(s) (after reviewing guidance in Section 6.6 for Grade ≥3 AEs lasting >7 – 14 days). Monitor laboratory parameters and clinically with endocrinology guidance.

ADL=activities of daily living; AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; FT4=free thyroxine; NCI=National Cancer Institute;TSH=thyroid-stimulating hormone

Additional Considerations:

- Be aware of the need to start corticosteroids first when planning hormone replacement therapy for multiple endocrine deficiencies.
- All subjects need instruction on doubling doses for illness (stress dosing) and a medical alert bracelet for adrenal insufficiency to trigger stress-dose corticosteroids by emergency medical services.
- Corticosteroid use can cause isolated central adrenal insufficiency.
- Work-up cannot be done with a simple AM cortisol in a subject on corticosteroids for other conditions.
- Laboratory confirmation of adrenal insufficiency should not be attempted until treatment with corticosteroids for other diseases is ready to be discontinued.
- For long-term exposure, consult endocrinology for recovery and weaning protocol using hydrocortisone.

12.2.9. Diabetes Management Algorithm

Rule out alternative non-immune related causes. Consider imaging as clinically indicated.

Diabetes management guidelines are provided in Table 20.

Investigators should review the section on endocrine toxicities in the ASCO, ESMO, NCCN, and SITC guidelines for additional details on diagnostic evaluation and management of diabetes and other immune-related endocrine AEs (Brahmer et al, 2018; Haanen et al, 2017; NCCN guidelines, 2020; Puzanov et al, 2017).

Table 20: Diabetes Management Algorithm

Grade of Hyperglycemia(NCI CTCAE v5.0)	Management	Follow-Up
Grade 1 Abnormal glucose above baseline with no medical intervention (Please note that the ASCO guidelines also include the absence of ketosis or laboratory evidence of T1DM in the definition of a Grade 1 event of immune checkpoint inhibitor related diabetes).	• May continue study drug(s) with close clinical follow-upand laboratory evaluation. • May initiate oral therapy for those with new-onset Type 2 diabetes. • Screen for Type 1 diabetes if appropriate, for example, acute onset with prior normal values or clinical concern for ketosis. • Consider endocrinology consultation.	<u>If worsens:</u> Treat as Grade 2 or Grade 3 – 4.
Grade 2 Change in daily management from baseline for a diabetic; oral antiglycemic agent initiated; workup for diabetes (Please note that the ASCO guidelines also include a fastingglucose value of 161 - 250 mg/dL (9 - 13.9 mmol/L), the presence of ketosis or evidence of T1DM at any glucose level in the definition of a Grade 2 event of immune checkpoint inhibitor related diabetes).	• Consider holding study drug(s) until glucose control isobtained. • Titrate oral therapy or add insulin for worsening control in Type 2 diabetes. • Administer insulin for type 1 diabetes (or as default therapy if there is confusion about type). • Urgent endocrine consultation for any subject with Type 1 diabetes. • Admit for type 1 diabetes if early outpatient evaluation is not available or signs of ketoacidosis are present.	<u>If worsens:</u> Treat as Grade 3 – 4. <u>When subject is clinically stable:</u> Re-start study drug(s). Monitor laboratory parameters and clinically with endocrinology guidance.

Grade of Hyperglycemia(NCI CTCAE v5.0)	Management	Follow-Up
Grade 3 - 4 Grade 3: Insulin therapy initiated; hospitalization indicated (Please note that the ASCO guidelines also include a fasting glucose value of 251-500 mg/dL (14 - 27.8 mmol/L) in the definition of a Grade 3 event of immune checkpoint inhibitor related diabetes). Grade 4: >500 mg/dL; Life-threatening consequences; urgent intervention indicated (Please note that the ASCO guidelines also include a fasting glucose value >500 mg/dL (>27.8 mmol/L) in the definition of a Grade 4 event of immune checkpoint inhibitor related diabetes).	• Hold study drug(s) until glucose control is obtained on therapy with reduction of toxicity to Grade 1 or less, review guidance in Protocol Section 6.5 for Grade ≥3 AEs lasting >14 days • Urgent endocrine consultation for all subjects. • Initiate insulin therapy for all subjects. • Admit for inpatient management: Concerns for developing diabetic ketoacidosis, symptomatic subjects regardless of diabetes type, new onset Type 1 diabetic ketoacidosis unable to see endocrinology.	If worsens: Re-evaluate with endocrinologist and other appropriate specialties. When symptoms resolve to baseline/subject is clinically stable: Consider re-starting study drug(s) (after reviewing guidance in Protocol Section 6.6 for Grade ≥3 AEs lasting >14 days). Monitor laboratory parameters and clinically with endocrinology guidance.

AE=adverse event; ASCO=American society of Clinical Oncology; CTCAE=Common Terminology Criteria for Adverse Events; NCI=National Cancer Institute

Additional Considerations

- Insulin therapy can be used as the default in any case with hyperglycemia.
- Long-acting therapy alone is not usually sufficient for T1DM, where half of daily requirements are usually given in divided doses as prandial coverage and half as long acting.
- Insulin doses will be lower in T1DM because of preserved sensitivity (total daily requirement can be estimated at 0.3 – 0.4 units/kg/day).
- In Type 2 diabetes, sliding-scale coverage with meals over a few days provides data to estimate a subject's daily requirements and can be used to more rapidly titrate basal needs.

12.2.10. Hepatic Adverse Event Management Algorithm

Rule out alternative non-immune related causes; corticosteroids should be initiated promptly for suspected irAEs and continued until an alternate etiology for a toxicity is determined or per the guidelines below and in Table 21. If a non-immune related cause is identified, treat accordingly, and continue budigalimab therapy as clinically appropriate. Consider imaging to evaluate for obstruction.

Diagnostic workup should include:

- Viral hepatitis serology, alcohol history, iron studies, evaluation for thromboembolic event, liver ultrasound, and cross-sectional imaging for potential liver metastasis from primary malignancy.
- If suspicion for primary autoimmune hepatitis is high, can consider anti-nuclear, anti-smooth muscle, and antineutrophil cytoplasmic antibodies. If the subject presents with elevated alkaline phosphatase alone, gamma-glutamyl transferase should be tested.
- For isolated elevation of transaminases, consider checking creatine kinase for other etiologies.

Investigators should review the section on GI/hepatic toxicities in the ASCO, ESMO, NCCN, and SITC guidelines for additional details on diagnostic evaluation of elevated liver tests and diagnostic evaluation and management of other immune-related GI/hepatic AEs (Brahmer et al, 2018; Haanen et al, 2017; NCCN guidelines, 2020; Puzanov et al, 2017).

Table 21: Hepatic Adverse Event Management Algorithm

Grade of Liver Test Elevation (NCI CTCAE v5.0)	Management	Follow-Up
Grade 1 ALT or AST > ULN - 3.0 × ULN if baseline wasnormal; 1.5 - 3.0 × baseline if baseline was abnormal and/or total bilirubin > ULN - 1.5 × ULN if baseline wasnormal; >1.0 - 1.5 × baseline if baseline was abnormal (Please note: the ASCO guidelines specify that Grade 1 events of immune checkpoint inhibitor related hepatitis are asymptomatic).	• Continue study drug(s) therapy per protocol with close clinical monitoring. • Supportive care for symptom control.	Monitor LFTs 1 – 2 times per week.<u>If worsens:</u> Treat as Grade 2, 3, or 4.
Grade 2 ALT or AST >3.0 - 5.0 × ULN if baseline was normal; >3.0 - 5.0 × baseline if baseline wasabnormal and/or Total bilirubin >1.5 - 3.0 × ULN if baseline wasnormal; >1.5 - 3.0 × baseline if baseline was abnormal (Please note: the ASCO guidelines specify that Grade 2 events of immune checkpoint inhibitor related hepatitis are asymptomatic).	• Delay study drug(s), review guidance in Protocol Section 6.5. • Increase frequency of clinical and LFT monitoring toevery 3 days. • For Grade 2 hepatic toxicity with symptoms, may administer corticosteroid (0.5 – 1 mg/kg/day prednisone or IV equivalent). • NOTE: Infliximab might not be the most appropriatetreatment option in the situation of immune- mediated hepatitis given the potential risk of idiosyncratic liver failure (Note: No clear evidence shows the liver toxicity from infliximab from other studies). • Stop unnecessary medications and any known hepatotoxic drugs.	<u>If returns to Grade 1 or baseline on prednisone ≤10 mg/day:</u> Resume study drug(s) therapy per protocol with routine monitoring. Taper steroids over at least 1 month. Consider prophylactic antibiotics for opportunistic infections. <u>If LFT elevation(s) persist >5 – 7 days or worsen</u>: Treat as Grade 3 or 4.

Grade of Liver Test Elevation (NCI CTCAE v5.0)	Management	Follow-Up
Grade 3 AST or ALT >5.0 - 20.0 × ULN if baseline was normal; >5.0 - 20.0 × baseline if baseline wasabnormal and/or Total bilirubin >3.0 - 10.0 × ULN if baseline was normal; >3.0 - 10.0 × baseline if baseline was abnormal (Please note: the ASCO guidelines specify that Grade 3 events of immune checkpoint inhibitor related hepatitis are also characterized by symptomatic liver dysfunction,fibrosis by biopsy, compensated cirrhosis, or reactivation of chronic hepatitis).	• Permanently discontinue study drug(s) therapy, review guidance in Protocol Section 6.5. • Immediately start 1 – 2 mg/kg/day IV methylprednisolone or equivalent. • If no improvement is achieved with corticosteroids, refer to hepatologist for further assessment including biopsy. • If corticosteroid refractory or no improvement after 3days, consider mycophenolate mofetil or azathioprine (if using azathioprine should test for thiopurine methyltransferase deficiency). • Laboratory studies (including LFTs) daily. • Consider hospital admission (especially if AST or ALT ≥8 × ULN and/or total bilirubin >3 × ULN). • Clinical monitoring every 1 – 2 days. • NOTE: Infliximab might not be the most appropriate treatment option in the situation of immune-mediated hepatitis given the potential risk of liver failure; alternatives include non–TNF-alpha agents as systemic immunosuppressants.	If LFTs improve: Corticosteroid taper can be attempted after 4 - 6 weeks when symptoms improveto Grade 1; re-escalate if needed; optimal duration unclear. If no improvement in >3 – 5 days, worsening LFTs or LFTs rebound: Treat as Grade 4.

Grade of Liver Test Elevation (NCI CTCAE v5.0)	Management	Follow-Up
Grade 4 AST or ALT >20.0 × ULN if baseline was normal; >20.0 × baseline if baseline was abnormal and/or Total bilirubin >10.0 × ULN if baseline was normal; >10.0 × baseline if baseline was abnormal (Please note: the ASCO guidelines specify that Grade 4 events of immune checkpoint inhibitor related hepatitis are also characterized by decompensated liver function: e.g., ascites, coagulopathy, encephalopathy, coma).	• Permanently discontinue study drug(s) therapy, review guidance in Protocol Section 6.5. • Administer 2 mg/kg/d methylprednisolone or IV equivalents. • If corticosteroid refractory or no improvement after 3 days, consider mycophenolate mofetil. • Monitor laboratories daily; consider inpatient monitoring. • Avoid the use of infliximab in the situation ofimmune-mediated hepatitis. • Hepatology consult if no improvement was achieved with corticosteroid. • Consider transfer to tertiary care facility if necessary.	If LFTs improve: Corticosteroid taper can be attempted after 4 - 6 weeks when symptoms improveto Grade 1 or less; re-escalate if needed; optimal duration unclear.

AE=adverse event; ALT=alanine aminotransferase; ASCO=American Society of Clinical Oncology; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; IV=intravenous; LFT=liver function test; NCI=National Cancer Institute; SAE=serious adverse event; TNF=tumor necrosis factor; ULN=upper limit of normal
Subjects on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to equivalent doses of oral corticosteroids.

* **Study drug(s) therapy may be delayed rather than discontinued if AST/ALT ≤8 × ULN and total bilirubin ≤5 × ULN, consult with study medical monitor in these cases prior torestarting study drug.**

A supplemental case report form should be completed by the investigator or designee for hepatic-related AEs that result in discontinuation or interruption of study drug, meet the criteria for an SAE, or involve the following laboratory criteria: 1) ALT and/or AST >8 × ULN, 2) ALT and/or AST >8 x ULN in conjunction with a total bilirubin >2 × ULN.

12.2.11. Skin Adverse Event Management Algorithm

Rule out alternative non-immune related causes; corticosteroids should be initiated promptly for suspected irAEs and continued until an alternate etiology for a toxicity is determined or per the guidelines below and in Table 22. If a non-immune related cause is identified, treat accordingly, and continue budigalimab therapy as clinically appropriate.

Diagnostic workup should include:

- Pertinent history and physical examination.
- Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease or unrelated primary skin disorder.
- If clinically indicated: laboratory hematology, liver, and kidney tests, directed serologic studies if an autoimmune condition is suspected, such as lupus or dermatomyositis, a Screening antinuclear antibody test, SS-A/Anti-Ro, SS-B/Anti-La if predominantly photodistributed/photosensitivity, antihistone, double-stranded DNA, and other relevant serologies.
- Consider expanding serologic studies or diagnostic workup if other autoimmune conditions are considered based on signs and symptoms.
- Skin biopsy.
- Consider clinical monitoring with use of serial clinical photography.
- Review full list of subject medications to rule out other drug-induced causes for photosensitivity.

The guidance in this appendix does not address all potential skin toxicities that may occur following treatment with an immune checkpoint inhibitor. Investigators should review the section on skin toxicities in the ASCO, ESMO, NCCN, and SITC guidelines for diagnostic evaluation and management of rash and diagnostic evaluation and management of other immune-related skin toxicities (Brahmer et al, 2018; Haanen et al, 2017; NCCN guidelines, 2020; Puzanov et al, 2017).

Table 22: Skin Adverse Event Management Algorithm

Grade of Rash*	Management	Follow-Up
Grade 1 Symptoms do not affect quality of life or are controlled with topical regimen and/or oral antipruritic.	• Consider holding study drug(s) therapy. • Symptomatic therapy (e.g., antihistamines, topical steroids, topical emollients). • Counsel avoidance of skin irritants and sun exposure. • Consider dermatology consultation and skin biopsy.	If persists >1 – 2 weeks, worsens or recurs: Treat as Grade 2, 3, or 4.
Grade 2 Inflammatory reaction that affects quality of life and requires intervention based on diagnosis.	• Consider holding study drug(s) and monitor weekly for improvement to Grade 1 or resolved (review guidance in Protocol Section 6.5 regarding duration of study drug(s) delays). • Consider initiating prednisone (or equivalent) at dosing 1 mg/kg. • Apply symptomatic therapy with topical emollients, oral antihistamines, and medium to high potency topical corticosteroids. • Consider dermatology consultation and skin biopsy.	If improves to Grade 1: Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections Discuss resumption of study drug(s) with medical monitor (if study drug(s) was held for Grade 2 event). If worsens: Treat as Grade 3 or 4.
Grade 3 As Grade 2 but with failure to respond to indicated interventions for a Grade 2 dermatitis.	• Hold study drug(s), review guidance in Protocol Section 6.5 for Grade ≥3 AEs lasting >14 days. • Consult dermatology. • Treat with topical emollients, oral antihistamines, and high-potency topical corticosteroids. • Initiate methylprednisolone (or equivalent) 1 – 2 mg/kg IV.	If improves to Grade 1: Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections. Discuss resumption of study drug(s) with medical monitor. If worsens: Treat as Grade 4.

Grade of Rash*	Management	Follow-Up
Grade 4 All severe rashes unmanageable with prior interventions and intolerable	• Discontinue study drug(s) therapy per protocol guidance in Protocol Section 6.5. • Consult dermatology. • Initiate methylprednisolone 1 – 2 mg/kg/day IV (or equivalent IVcorticosteroid dose). • Admit subject to hospital and monitor closely for progression to severe cutaneous adverse reaction.	If improves to Grade 1: Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections. If no improvement: Re-consult dermatologist (or other appropriate specialty) and consider additional therapy per local guidelines.

AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; IV=intravenous; NCI=National Cancer Institute

Subjects on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to equivalent doses of oral corticosteroids.

* Grading according to CTCAE is a challenge for skin toxicities. Instead, severity may be based on body surface area, tolerability, morbidity, and duration. Refer to NCI CTCAEversion 5.0 for grading of specific skin toxicities other than rash.

12.2.12. Severe Cutaneous Adverse Reactions Management Algorithm

The following guidelines and Table 23 are provided to manage potential severe cutaneous adverse reactions (SCAR), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis, drug reaction with eosinophilia and systemic symptoms (DRESS) and drug-induced hypersensitivity syndrome (DIHS).

Diagnostic work-up:

- Total body skin examination with attention to examining all mucous membranes as well as complete review of systems
- Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease
- A biologic checkup, including a CBC with differential test, and liver and kidney function tests, including urinalysis, in addition to the blood work; if the subject is febrile, blood cultures should be considered as well
- Skin biopsies to assess for full-thickness epidermal necrosis, as is seen in SJS/TEN, as well as other possible etiologies like paraneoplastic pemphigus or other autoimmune blistering dermatoses or other drug reactions, such as acute generalized exanthematous pustulosis
- Consider following subject's clinical course closely, using serial clinical photography
- If mucous membrane involvement or blistering on the skin is observed, consider early admission to a burn center for further monitoring and management
- NOTE: In cases of suspected SJS, TEN or any mucous membrane involvement, permanently discontinue budigalimab and monitor closely for improvement, regardless of grade

Monitoring complicated cutaneous adverse drug reactions:

- Review of systems: Skin pain (like a sunburn), fevers, malaise, myalgias, arthralgias, abdominal pain, ocular discomfort or photophobia, sores or discomfort in the nares, sores or discomfort in the oropharynx, odynophagia, hoarseness, dysuria, sores, or discomfort in the vaginal area for women or involving the meatus of the penis for men, sores in the perianal area, or pain with bowel movements
- Physical examination:
  - Vital signs and a full skin examination specifically evaluating all skin surfaces and mucous membranes (eyes, nares, oropharynx, genitals, and perianal area)
  - Assess for lymphadenopathy, facial or distal extremity swelling (may be signs of DIHS/DRESS)
  - Assess for pustules or blisters or erosions in addition to areas of "dusky erythema," which may feel painful to palpation

- To assess for a positive Nikolsky sign, place a gloved finger tangentially over erythematous skin and apply friction parallel to the skin surface
  - Nikolsky sign is positive if this results in detached or sloughing epidermis demonstrating poor attachment of the epidermis to the dermis, which is the case in some autoimmune disorders (e.g., pemphigus) and SJS/TEN

Investigators should review the section on skin toxicities in the American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), National Comprehensive Cancer Network (NCCN), and Society for Immunotherapy and Cancer (SITC) guidelines for additional details on diagnostic evaluation and management of skin toxicities following treatment with immune checkpoint inhibitors. (Brahmer et al, 2018; Haanen et al, 2017; NCCN guidelines, 2020; Puzanov et al, 2017).

Table 23: Severe Cutaneous Adverse Reactions Management Algorithm

Grade of Severe Skin Change	Management	Follow-Up
All Grades	**In cases of suspected SJS, TEN or any mucous membraneinvolvement, permanently discontinue budigalimab treatment and monitor closely for improvement, regardless of grade.**	As specified for each toxicity grade below.
Grade 1	• There is no Grade 1 category for SCARs.	• If lower BSA is involved with bullae or erosions,there should remain a high concern that reaction will progress to Grade 3 or Grade 4.
Grade 2 Morbilliform ("maculopapular") exanthem covering 10% - 30% BSA with systemic symptoms, lymphadenopathy, or facial swelling	• Hold budigalimab and monitor patients closely every 3 days with G2 irAEs for progression to involvement of greater BSA and/or mucous membrane involvement. • Consider following patients closely using serial photography. • Initiate therapy with topical emollients, oral antihistamines, and medium- to high strength topical corticosteroids. • Consider initiation of prednisone (or equivalent) • 0.5 – 1 mg/kg tapered over at least 4 weeks	<u>If rash and clinical symptoms resolve completely:</u> • Resume routine monitoring. • Consider re-starting budigalimab therapy per following discussion with Sponsor/Medical Monitor <u>If symptoms worsen:</u> • Treat as Grade 3 or Grade 4

Grade of Severe Skin Change	**Management**	**Follow-Up**
Grade 3 Skin sloughing covering <10% BSAwith mucosal involvement associated signs (e.g., erythema, purpura, epidermal detachment, mucous membrane detachment)	• Permanently discontinue budigalimab therapy and consult with dermatology. • Treat skin with topical emollients and other petrolatum emollients, oral antihistamines, and high-strength topical corticosteroids; dimethicone may also be offered as an alternative to petrolatum. • Administer IV (methyl)prednisolone (or equivalent) 0.5 – 1 mg/kg and convert to oral corticosteroids on response, wean over at least 4 weeks • Admit to burn unit and/or consult wound services with attention to supportive care, including fluid and electrolyte balance, minimizing insensible water losses, and preventing infection. • Given the immune mechanism of action of these medicines, use of immune suppression is warranted and should be offered • For mucous membrane involvement of SJS or TEN,appropriate consulting services should be offered to guide management in preventing sequelae fromscarring (e.g., ophthalmology; ear, nose, and throat; urology; gynecology; etc., as appropriate)	<u>If returns to Grade 2:</u> • Taper steroids over at least 1 month <u>If symptoms worsen:</u> • Re-evaluate with appropriate consultative services and treat as Grade 4

Grade of Severe Skin Change	Management	Follow-Up
Grade 4 Skin erythema and blistering/sloughing covering ≥10% BSA with associated signs (e.g., erythema, purpura, epidermal detachment, mucous membrane detachment) and/or systemic symptoms and concerning associated bloodwork abnormalities(e.g., liver function test elevations inthe setting of DRESS/DIHS)	• Permanently discontinue budigalimab. • Admit patient immediately to a burn unit or ICU with consulted dermatology and wound care services. • Consider further consultations based on management of mucosal surfaces (e.g., ophthalmology; urology; gynecology; ear, nose, and throat surgery; etc.) • Initiate IV (methyl)prednisolone (or equivalent) 1 – 2 mg/kg, tapering when toxicity resolves to normal • IVIG or cyclosporine may also be considered in severe or corticosteroid unresponsive cases • Consider pain/palliative consultation and/or admission in patients presenting with DRESS manifestations	• Follow subject until resolution of toxicity.

BSA=body surface area; CTCAE=Common Terminology Criteria for Adverse Events; DIHS=drug-induced hypersensitivity syndrome; DRESS=drug reaction with eosinophilia and systemic symptoms; ICU=intensive care unit; IV=intravenous; IVIG=intravenous immunoglobulin; NCI=National Cancer Institute; SJS=Stevens-Johnson syndrome (SJS); TEN=toxic epidermal necrolysis

Additional Considerations:

- The usual prohibition of corticosteroids for SJS is not relevant here, as the underlying mechanism is a T cell immuno-directed toxicity. Adequate suppression is necessary with corticosteroids or other agents and may be prolonged in cases of DRESS/DIHS.
- Subjects on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to equivalent doses of oral corticosteroids.

12.2.13. Neurologic Adverse Event Management Algorithm

Rule out non-inflammatory causes; corticosteroids should be initiated promptly for suspected irAEs and continued until an alternate etiology for a toxicity is determined or per the guidelines below and in Table 24. If a non-inflammatory cause is identified, treat accordingly, and continue budigalimab (ABBV-181) therapy as clinically appropriate.

The guidance in this appendix describes management of peripheral motor or sensory neuropathy and does not address all potential neurologic AEs that may occur following treatment with an immune checkpoint inhibitor (i.e., myasthenia gravis, Guillain-Barre Syndrome, autonomic neuropathy, aseptic meningitis, encephalitis, transverse myelitis). Investigators should review the section on nervous system toxicities in the ASCO, ESMO, NCCN, and SITC guidelines for diagnostic evaluation and management of neuropathy and diagnostic evaluation and management of other immune-related neurologic toxicities (Brahmer et al, 2018; Haanen et al, 2017; NCCN guidelines, 2020; Puzanov et al, 2017).

Please note that, per the ASCO guidelines on management of irAEs following immune checkpoint inhibitor therapy, Grade 3 or 4 peripheral neuropathy should be managed per the guidance regarding treatment-emergent Guillain-Barre Syndrome and investigators should consult the ASCO guidelines for additional interventions (Brahmer et al, 2018).

Table 24: Neurologic Adverse Event Management Algorithm

Grade of Peripheral Neuropathy* (NCI CTCAE v5.0)	Management	Follow-Up
Grade 1 Motor: Asymptomatic; clinical or diagnosticobservations only. Sensory: Asymptomatic; loss of deep tendon reflexes or paresthesia. (Note: Any cranial nerve abnormality should be managed as Grade 2)	• Continue study drug(s) therapy. • Monitor weekly. • Consider neurology consultation.	Continue clinical monitoring. If worsens: Treat as Grade 2 or Grade 3 – 4.
Grade 2 Motor or Sensory: Moderate symptoms; limiting instrumental ADL.	• Delay study drug(s) therapy. • Consult neurology. • Treat symptoms per local guidance (i.e., Neurontin, pregabalin, or duloxetine forpain). • Initiate prednisone 0.5 – 1 mg/kg/day IV (or equivalent IV corticosteroid dose). • Add prophylactic antibiotics for opportunistic infections.	If improves to Grade 1: Resume routine monitoring. Resume study drug(s) therapy per protocol when symptoms improve to baseline following discussion with medical monitor. If symptoms worsen: Treat as Grade 3 – 4.

Grade of Peripheral Neuropathy* (NCI CTCAE v5.0)	Management	Follow-Up
Grade 3 – 4 Motor or Sensory Grade 3: Severe symptoms; limiting self-care ADL. Grade 4: Life-threatening consequences; urgent intervention indicated. (The ASCO guidelines specify that Grade 3 - 4 eventsof immune checkpoint inhibitor-related peripheral neuropathy are also characterized by severe symptoms, limitations in self-care with aids warranted, weakness limiting walking or respiratory problems [e.g., leg weakness, foot drop, rapidly ascending sensory changes]). Note: Grade 3 - 4 toxicity may be due to Guillain-Barre Syndrome and should be managed as such.	• Discontinue study drug(s) therapy, review guidance in Protocol Section 6.5 for Grade ≥3 AEs lasting >14 days. • Consult neurology. • Admit subject to hospital. • Treat symptoms per local guidance. • Initiate methylprednisolone 2 – 4 mg/kg/day IV and proceed as per Guillain-Barre Syndrome management (see ASCO guidelines). • Add prophylactic antibiotics for opportunistic infections.	If returns to Grade 2: Taper steroids over at least 1 month. If symptoms worsen: Re-evaluate with neurologist, consider additional imaging as clinically indicated.

ADL=activities of daily living; AE=adverse event; ASCO=American Society of Clinical Oncology; CTCAE=CommonTerminology Criteria for Adverse Events; IV=intravenous; NCI=National Cancer Institute

Subjects on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) once sustainedclinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to equivalent doses of oral corticosteroids.

* The NCI-CTCAE version 5.0 and the ASCO guidelines, on management of immune related AEs following treatment with immune checkpoint inhibitors should be consulted for descriptions of other specific neurologic toxicities andtheir management.

12.3. Appendix 3: RECIST Version 1.1

Tumor response will be assessed according to RECIST 1.1 (Eisenhauer et al, 2009), as described below.

Measurability of Tumor at Baseline

At baseline, tumor lesions/lymph nodes will be categorized as measurable or nonmeasurable as follows:

- **Measurable**

  Tumor lesions: Must be accurately measured in ≥1 dimension (longest diameter in the plane of measurement to be recorded) with a minimum size of:

  – 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)

  – 10 mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as nonmeasurable)

  – 20 mm by chest X-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

- **Nonmeasurable**

  – All other lesions (or disease sites), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis)

  – Lesions considered truly nonmeasurable include the following: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

Tumor Response Evaluation

Baseline Documentation of Target and Nontarget Lesions

- **Target lesions**

  – When >1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions

  – It may be the case that, on occasion, the largest lesion, which can be measured reproducibly, should be selected

- **Nontarget lesions**

  – All other lesions (or disease sites), including pathological lymph nodes, should be identified as nontarget lesions

– It is possible to record multiple nontarget lesions involving the same organ as a single item (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases")

Evaluation of Target Lesions

Target lesions will be evaluated, and response recorded as defined in Table 25.

Table 25: Response Based on Evaluation of Target Lesions at Each Assessment

Complete response	Disappearance of all target lesions; if a pathologic lymph node, reduction in the shortest axis to <10 mm[a]
Partial response[b]	≥30% decrease in the sum of the diameters of target lesions relative to the baseline sum diameters[c]
Stable disease[b,d]	Neither a sufficient reduction to qualify as a partial response nor a sufficient increase to qualify as progression[c]
Progressive disease[b]	≥20% increase in the sum diameters relative to the smallest sum diameters recorded (including the baseline sum diameters) in conjunction with an increase of at least 5 mm in that smallest sum diameters or the appearance of 1 or more new lesions[c,e]

[a] For each pathologic lymph node considered a target lesion, the node must have a short axis measuring <10 mm to be considered as a complete response. In such cases, the sum diameters may not be zero (as a normal lymph node can have a short axis of <10 mm).

[b] For each pathologic lymph node considered a target lesion, the measurement of the short axis of the node is to be included in the sum diameters when determining partial response, stable disease, and progression.

[c] In this study, the "baseline sum diameter" is calculated based on the lesion measurements obtained at Screening.

[d] Duration of stable disease is measured from the date of the loading dose/first dose of investigational product until criteria for progressive disease are met based on the smallest sum diameters recorded (including the baseline sum diameters).

[e] The finding of a new lesion should be unequivocal and not possibly attributable to a difference in imaging modality or scanning technique. Post-baseline, fluorodeoxyglucose positron emission tomography (FDG-PET) may be useful in assessing new lesions apparent on computed tomography (CT) scan.

Evaluation of Nontarget Lesions

Nontarget lesions will be evaluated, and response recorded as defined in Table 26.

Table 26: Response Based on Evaluation of Nontarget Lesions at Each Assessment

Complete response	Disappearance of all nontarget lesions; all lymph nodes must be nonpathologic in size (i.e., <10 mm on the short axis)
Not complete response or not progressive disease	Persistence of 1 or more nontarget lesions
Progressive disease	Unequivocal progression[a] of any existing nontarget lesion or the appearance of 1 or more new lesions[b]

[a] The subject should stop investigational product, even in the presence of a partial response or stable disease, based on an assessment of target lesions.

[b] The finding of a new lesion should be unequivocal and not possibly attributable to a difference in imaging modality or scanning technique. Post-baseline, fluorodeoxyglucose positron emission tomography (FDG-PET) may be useful in assessing new lesions apparent on computed tomography (CT) scan.

New Lesions

The appearance of new malignant lesions denotes PD; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, i.e., not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (e.g., some "new" bone lesions may be simply

healing or flare of pre-existing lesions). This is particularly important when the subject's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

Evaluation of Overall Response

Overall response based on the evaluation of target and nontarget lesions will be determined as shown in Table 27.

Table 27: Evaluation of Overall Response at Each Assessment

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
Complete response	Complete response	No	Complete response
No target lesion[a]	Complete response	No	Complete response
Complete response	Not evaluable[b]	No	Partial response
Complete response	Not complete response/ non-progressive disease	No	Partial response
Partial response	Non-progressive disease and not evaluable[b]	No	Partial response
Stable disease	Non-progressive disease and not evaluable[b]	No	Stable disease
Not all evaluated	Non-progressive disease	No	Not evaluable
No target lesion[a]	Not all evaluated	No	Not evaluable
No target lesion[a]	Non-complete response/ non-progressive disease	No	Non-complete response/ non-progressive disease
Progressive disease	Any	Yes or No	Progressive disease
Any	Progressive disease	Yes or No	Progressive disease
Any	Any	Yes	Progressive disease
No target lesion[a]	Unequivocal progressive disease	Yes or No	Progressive disease
No target lesion[a]	Any	Yes	Progressive disease

[a] Defined as no target lesions at baseline.

[b] Not evaluable is defined as either when no or only a subset of lesion measurements are made at an assessment.

12.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

12.4.1. Definitions

12.4.1.1. Definition of Adverse Event (AE)

AE Definition
• An AE is any untoward medical occurrence in a subject, temporally associated with the use of the investigational product, whether or not considered related to the investigational product. NOTE: An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational product.
Events Meeting the AE Definition
• Any abnormality or deterioration in a laboratory test result (hematology, clinical chemistry, or urinalysis) or other safety assessment (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from baseline or are considered clinically significant in the medical and scientific judgment of the Investigator. • Exacerbation of a chronic or intermittent pre-existing condition including an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after investigational product administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concomitant medication. • Serious events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study procedures (e.g., Screening invasive procedures, such as biopsies, discontinuation of investigational product). • Any new cancer (that is not a condition of the study).
Events NOT Meeting the AE Definition
• Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that does not worsen. • Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened. • Progression of the cancer under study

12.4.1.2. Definition of Serious Adverse Event (SAE)

If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met.

SAE Definition
An SAE is defined as any AE that suggests a significant hazard, contraindication, side effect, or untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained at the hospital or emergency room for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Hospitalization is defined as an inpatient admission, regardless of the length of stay, even if the hospitalization is a precautionary measure for continued observation. Note: Hospitalizations for the following reasons are not considered SAEs in this study: 1 A visit to the emergency room or another hospital department of <24 hours that does not result in admission (unless considered an important medical or life-threatening event) 2 Elective surgery planned prior to signing a consent 3 Admissions as per protocol for a planned medical/surgical procedure 4 Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy) 5 Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases. 6 Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
d. Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect This refers to offspring of a subject exposed to the investigational product regardless of timing to diagnosis. Any spontaneous abortion should be reported in the same fashion (as the Sponsor considers spontaneous abortions to be medically significant).

f. Other important medical events

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

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

12.4.1.3. Definition of Unexpected Adverse Event

Unexpected AE Definition

- Any AE, the specificity or severity of which is not consistent with the current Investigator's Brochure. Expected means that the event has previously been observed with the investigational product and is identified and/or described in the current Investigator's Brochure. It does not mean that the event is expected with the underlying disease(s), co-morbidities, or concomitant medications.

12.4.1.4. Definition of Treatment-emergent Adverse Event

Treatment-emergent AE Definition

- Any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding that is considered to be clinically significant), syndrome, or disease that either occurs during the study, having been absent at baseline, or if present at baseline, appears to have worsened in severity or frequency, whether or not the event is considered related to the investigational product.

12.4.2. Additional Events Reported in the Same Manner as a Serious Adverse Event

Additional Events Reported in the Same Manner as an SAE

- In addition to the SAE criteria in Section 8.3, AEs meeting any of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.
  - Is a new cancer (that is not a condition of the study)
  - Is associated with an overdose
  - Pregnancy (as specified in Section 8.3.5)
  - Adverse events of special interest (AESIs; defined in Section 8.3.7)

12.4.3. Recording Adverse Events and Serious Adverse Events

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. Only a single AE term should be recorded for the event.
- The Investigator will record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the Investigator to send photocopies of the subject's medical records to the Sponsor in lieu of completion of the Adverse Event/Serious Adverse Event eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Severity

- The terms "severe" and "serious" are not synonymous. An event is defined as serious when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe. Severity (intensity) and seriousness need to be independently assessed for each AE recorded on the eCRF.
- The Investigator will make an assessment of intensity for each AE and SAE (and another reportable safety event) according to the NCI CTCAE v5.0, which can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. The following grading will be used for assessing intensity of AEs not specifically listed in the NCI CTCAE:
  - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
  - Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
  - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
  - Grade 4: Life-threatening consequences; urgent intervention indicated.
  - Grade 5: Death related to AE.
- Any AE that changes CTCAE grade over the course of a given episode (i.e., persistent AE) will have each change of grade recorded on the Adverse Event eCRF page.

Assessment of Causality

- The Investigator is obligated to assess the relationship between investigational product and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use his/her clinical judgment, knowledge of the subject, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine the relationship.
- The following guidance will be considered and investigated:
  - Temporal relationship of the event onset to investigational product administration
  - The course of the event, with special consideration of the effects of dose reduction, discontinuation of the investigational product, or reintroduction of the investigational product (as applicable)
  - Known association of the event with the investigational product or with similar treatments
  - Known association of the event with the disease under study

  - Presence of risk factors in the subject or use of concomitant medications known to increase the occurrence of the event
  - Presence of non-treatment-related factors that are known to be associated with the occurrence of the event
- The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the Investigator always assess causality for every event before the initial transmission of the SAE data to the Sponsor.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- For studies in which multiple agents are administered as part of a combination regimen, the Investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (i.e., to all agents in the regimen). However, causality attribution may be assigned to a single agent if, in the Investigator's opinion, there are sufficient data to support the full attribution of the AE to the single agent.

Is the AE suspected to be caused by the investigational product based on facts, evidence, science-based rationales, and clinical judgment?

- Yes: There is a plausible temporal relationship between the onset of the AE and administration of the investigational product, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the investigational product; and/or the AE abates or resolves upon discontinuation of the investigational product or dose reduction and, if applicable, reappears upon rechallenge.
- No: An AE will be considered related, unless it fulfills the following criteria: Evidence exists that the AE has an etiology other than the investigational product (e.g., pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to administration of the investigational product (e.g., cancer diagnosed 2 days after the first dose of investigational product).

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the eCRF.
- The Investigator will submit any updated data related to SAEs to the Sponsor within 24 hours of receipt of the information.

12.4.4. Reporting of Adverse Events, Serious Adverse Events, and Other Reportable Safety Events to the Sponsor

Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

- The primary mechanism for reporting Adverse Events to the Sponsor will be completion of an Adverse Event eCRF in EDC. If the Adverse Event meets seriousness criteria, then reporting via EDC (and signing the form) must be done within 24 hours of becoming aware of the event.
- If the event meets seriousness criteria and it is not possible to access the EDC system, call the PPD hotline and/or fax the completed paper SAE form within 24 hours of awareness (see contact information below). When the EDC system is available, any SAE information provided via telephone or in the paper SAE form should then be reflected in EDC as soon as possible.
    - Safety Hotline Number
        - North America: +1 910-558-7104
        - EMEA/APAC: 0044 1223 374240
    - Facsimile of completed paper SAE form
        - North America: +1 888-488-9697
        - EMEA/APAC: 00441223 374240
- Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
- If a site receives updated data on a previously reported SAE, then the site can report this information by updating the relevant Adverse Event eCRF in EDC and signing the form. If it is not possible to access the EDC system, call the PPD hotline and/or fax the completed paper SAE form (utilizing the initial and follow-up check boxes)
- Initial notification via facsimile and telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting timeframes.

12.4.5. Additional Reporting Considerations

AE and SAE Recording for Special Circumstances

Diagnosis versus Signs and Symptoms

- A diagnosis (if known) or cause of death should be recorded on the Adverse Event eCRF page rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases).
- If a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded separately on the Adverse Event eCRF page.
- If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

AEs That Are Secondary to Other Events

- In general, AEs that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of serious secondary events. A medically significant secondary AE that is separated in time from the initiating event should be recorded as

an independent event on the Adverse Event eCRF page. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe GI hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

- All AEs should be recorded separately on the Adverse Event eCRF page if it is unclear as to whether the events are associated.

Persistent or Recurrent AEs

- A persistent AE is one that extends continuously, without resolution, between subject evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF page. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported.
- If a persistent AE becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF page, and details regarding any increases or decreases in severity will be captured on the Adverse Event eCRF page.
- If the event becomes serious, it should be reported to the Sponsor as an SAE, and the Adverse Event eCRF page should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to SAEs.
- A recurrent AE is one that resolves between subject evaluation timepoints and subsequently recurs. Each recurrence of an AE should be recorded as a separate event on the Adverse Event eCRF page.

Abnormal Laboratory Values

- A clinical laboratory test value must be reported as an AE if it meets any of the following criteria:
  - Is accompanied by clinical symptoms
  - Results in a change in investigational product (e.g., dose modification, treatment interruption, or treatment discontinuation)
  - Results in a medical intervention or change in concomitant medication
  - Is clinically significant in the Investigator's judgment

Abnormal Vital Sign Values

- Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.
- If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF page.
- Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF page (see above for details on recording persistent

AEs).

Abnormal Liver Function Tests

- The finding of an elevated ALT or AST (>3 x baseline value) in combination with either an elevated total bilirubin (>2 x ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, Investigators must report as an AE the occurrence of either of the following:
  - Treatment-emergent ALT or AST >3 x baseline value in combination with total bilirubin >2 x ULN (of which ≥35% is direct bilirubin)
  - Treatment-emergent ALT or AST >3 x baseline value in combination with clinical jaundice
- The most appropriate diagnosis or, if a diagnosis cannot be established, the abnormal laboratory values should be recorded on the Adverse Event eCRF page.

Lack of Efficacy or Worsening of Underlying Disease

- Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST criteria. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through the use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE.

Deaths

- All deaths that occur during the protocol-specified AE reporting period, regardless of relationship to the investigational product, must be recorded on the Death eCRF page and immediately reported to the Sponsor (see Section 8.3.1), unless the death is attributed to progression of underlying disease.
- Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF page. Generally, only one such event should be reported.
- If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the Adverse Event eCRF page.
- If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.
- The term "sudden death" should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").
- If the death is attributed to progression of the underlying disease, "underlying disease" should be recorded on the Death eCRF page.
- Deaths that occur after the AE reporting period should be reported as described in Section 8.3.6.

Pre-existing Medical Conditions

- A pre-existing medical condition is one that is present at the Screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF page.

  A pre-existing medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse

Event eCRF page, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

AEs Associated with Overdose or Error in Drug Administration

- An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of investigational product is not itself an AE, but it may result in an AE. All AEs associated with an overdose or incorrect administration of investigational product should be recorded on the Adverse Event eCRF page.
- If the associated AE fulfills seriousness criteria, the event should be reported to the Sponsor as an SAE.

12.5. Appendix 5: Pregnancy Information

12.5.1. Pregnancy Testing

- Women of childbearing potential should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test.
- Additional pregnancy testing should be performed as specified in the Schedule of Activities (Section 1.3).
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

12.5.2. Collection of Pregnancy Information

12.5.2.1. Male Subjects with Partners who Become Pregnant

- The Investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. This applies only to male subjects who receive the investigational product.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

12.5.2.2. Female Subjects who Become Pregnant

- To report a pregnancy, submit a complete Pregnancy – Initial Report form via fax or call the PPD hotline (see below contact information) within 24 hours of awareness. Any updates to the event should be reported using the Pregnancy Follow-Up Report Form using the same channel.
  - PPD Hotline
  - NA: +1 910-558-7104
  - EMEA/APAC: 0044 1223 374240
  - Facsimile completed Pregnancy Report Form
  - NA: +1 888-488-9697
  - EMEA/APAC: 0044 1223 374240
- The Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a subject's pregnancy. The subject will be followed to determine the outcome of the

pregnancy. The Investigator will collect follow-up information on the subject and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy-related SAE considered reasonably related to the investigational product by the Investigator will be reported to the Sponsor as described in Section 8.3.5. While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.
- Any female subject who becomes pregnant while participating in the study will discontinue investigational product or be withdrawn from the study.

12.6. Appendix 6: Cockcroft-Gault and CKD-EPI Formulas

Cockcroft-Gault Formula:

Male: Creatinine Clearance Value = [(140 – age) (weight kg) / (72 X Scr)]

Female: Creatinine Clearance Value = 0.85 * [(140 – age) (weight kg) / (72 X Scr)]

Scr = Serum creatinine
Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.

CKD-EPI Equation:

$eGFR_{cr} = 142 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.200} \times 0.9938^{Age} \times 1.012$ [if female]

where:
S_{cr} = standardized serum creatinine in mg/dL
κ = 0.7 (females) or 0.9 (males)
α = -0.241 (female) or -0.302 (male)
min (S_{cr}/κ, 1) is the minimum of S_{cr}/κ or 1.0
max (S_{cr}/κ, 1) is the maximum of S_{cr}/κ or 1.0
Age (years)

CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; eGFR=estimated glomerular filtration rate; max=maximum; min=minimum; S_{cr}=serum creatinine.
Source: Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.

12.7. Appendix 7: Protocol Amendment History

Version Number	Section Number or Title	Description of Change	Reason for Change
1.2	Title Page; Protocol, Approval Page, Protocol Acceptance Form	Addition of EU CT Number	Required for submission to EUCTR
1.1	Section 1.3 (footnote [b]); Section 5.1; Section 8.3.5	Updated contraception requirement to include until "6 months (180 days) after the last administration of any study treatment".	To align contraception requirement for all study treatment to nab-paclitaxel and gemcitabine prescribing information.
1.1	Section 1.3 (footnote [p]); Section 6.1;	Specified monitoring for a minimum of 60 minutes following completion of TTX-030 and/or budigalimab infusions.	Specified monitoring period for acute infusion-related toxicities.
1.1	Section 1.3 (footnote [n]); Section 8.8	Clarification that biopsies should only be performed if deemed safe by the Investigator.	Ensure appropriate risk mitigation for subjects.
1.1	Section 4.1	Addition of safety assessment and study stopping rules at 6 and 30 patients per arm.	Ensure appropriate risk/benefit for 1L PDAC treatment.
1.1	Section 6.5.1	Removed duplication of safety review of the first 6 subjects.	Replaced with stopping rule framework in Section 4.1.
1.1	Section 6.5.1.1	Added guidance for diagnosis and management of cytokine release syndrome including the use of corticosteroids and tocilizumab.	CRS is an AESI in the current study.
1.1	Section 8.1.2	Removed language that permitted treatment of subjects beyond disease progression per RECIST 1.1.	Ensure appropriate transition to subsequent treatment.
1.0	Original	NA	NA

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