TITLE PAGE

Protocol Title:	Phase 1/1b Study to Evaluate the Safety and Activity of TTX-030 (Anti-CD39) in Combination with Pembrolizumab or Budigalimab and/or Chemotherapy in Subjects with Advanced Solid Tumors
Protocol Number:	TTX-030-002
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]
Regulatory Agency Identifying Number(s): **IND Number:**	138313
Protocol Version, Date:	Version 1.0, 10 February 2020
	Version 2.0, 06 July 2020
	Version 3.0, 22 October 2020
	Version 4.0, 06 April 2021
	Version 5.0, 09 September 2021

CONFIDENTIAL

PROTOCOL APPROVAL PAGE

PROTOCOL TITLE:

Phase 1/1b Study to Evaluate the Safety and Activity of TTX-030 (Anti-CD39) in Combination with Pembrolizumab or Budigalimab and/or Chemotherapy in Subjects with Advanced Solid Tumors

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Protocol Version, Date:	Version 1.0, 10 February 2020 Version 2.0, 06 July 2020 Version 3.0, 22 October 2020 Version 4.0, 06 April 2021 Version 5.0, 09 September 2021

Approval of protocol by Sponsor:

[redacted]

PROTOCOL ACCEPTANCE FORM

PROTOCOL TITLE:

Phase 1/1b Study to Evaluate the Safety and Activity of TTX-030 (Anti-CD39) in Combination with Pembrolizumab or Budigalimab and/or Chemotherapy in Subjects with Advanced Solid Tumors

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IND Number:	138313
Sponsor:	Trishula Therapeutics, Inc. 2268 Westborough Boulevard, Suite 302 #263 South San Francisco, CA 94080
Medical Monitor:	[redacted]
Protocol Version, Date:	Version 5.0, 09 September 2021

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	10 February 2020
Version 2.0, Amendment 1	06 July 2020
Version 3.0, Amendment 2 (Trishula)	22 October 2020
Version 4.0, Amendment 3 (Trishula)	06 April 2021
Version 5.0, Amendment 4 (Trishula)	09 September 2021

Amendment Version 5.0 (09 September 2021)

Overall Rationale for the Amendment:

Section #	Description of Change	Brief Rationale
Entire document	Minor spelling, grammar, punctuation, capitalization, and other formatting edits were made throughout the document	Consistency
Title Page, Protocol Approval Page, Protocol Acceptance Page	Updated Sponsor address and Medical Monitor	Change in address and personnel
Table 1	Updated column headings to add “first dose” after loading dose. Added the following footnotes: • For Cohort 12, the loading dose visit is not applicable; baseline and C1D1 assessments may be combined. • Pregnancy test language • PK sample collection language • Tumor biopsy language • AE language • Added that concomitant medication information would be collected from 30 days prior to Screening.	To cover cohorts that did not include a loading dose. To clarify visits for Cohort 12 For clarification For clarification For clarification For clarification To collect concomitant medications to verify eligibility criteria
Table 2 and Table 3	Removed C1D2, C1D3, and C1D15 visits, updated PK rows, and updated PK footnotes	Due to removal of PK/ADA/PD samples at these time points (since these assessments were primarily for the safety lead-in cohorts), the visits have been removed to reduce patient burden.
Table 2 and Table 3	Decreased frequency of ECG testing and updated ECG footnotes	Since ECGs were obtained at the time of PK/ADA/PD samples and PK/ADA/PD sampling was decreased, ECG testing was decreased
Table 2	Removed PD plasma (Strek tubes) sampling	To streamline visit procedures
Table 2	Added Cohort 11 and 12 to table	To align with updated study design
Table 2	Updated assessments: - Changed PE to symptom-directed PE for C1D1, C1D15, C2D15, C3D15, and CXD15	To streamline visit procedures

Section #	Description of Change	Brief Rationale
	and removed symptom-directed PE on visits where PE is performed. - Removed ECOG, urinalysis, pregnancy test assessment on C1D8, C1D15, C2D8, C2D15, C3D8, C3D15, and CXD15. - Added row for HbA1c on CXD1.	
Table 3	Removed C2D8 visit	To reduce patient burden
Table 4 and Table 5	Removed tables since Table 2 and Table 3 were updated to capture relevant details.	Conciseness and to align with updated frequency of PK and ECG testing
Section 1.2	Figure 1 Study Schema: Updated to reflect changes in study design	To align with new cohorts and discontinued cohorts
Table 4, Section 5.1, and Section 8.3.5	Added follow-up contraception check until 180 days after the lase dose of gemcitabine/nab-paclitaxel	To align with continued effective contraception, use per approved labels
Section 2.2.1.1	Updated rationale for combining TTX-030 with budigalimab and gemcitabine/nab-paclitaxel.	Added as context for changes to protocol
Section 2.2.10	Added explanation that combination of TTX-030 + budigalimab + mFOLFOX6 combination in Cohort 1 (triplet) was deemed safety with no DLTs observed based on evaluation of safety profile	Supports safety profile of combination therapies
Section 2.2.11	Added Section 2.2.11 'Rationale for Combining TTX-030 and Gemcitabine plus nab-Paclitaxel'	Demonstrates effectiveness of TTX-030 in supporting other combination therapies with different mechanism of action
Section 3 and Section 9.3.2	Adjusted description of objective response rate to included unconfirmed CR and PR, Removed SD for >4 months and replaced with SD only from description of disease control rate.	Updated definitions.
Section 4.1.1.2	Discontinued randomization to Cohort 3 Arm A (GEC treated with TTX-030 + mFOLFOX6)	A checkpoint inhibitor (nivolumab) was approved in April 2021 for front line treatment of GEC with chemotherapy. Due to the new standard of care for front line therapy, it is no longer acceptable to randomize subjects to an arm without a checkpoint inhibitor in addition to chemotherapy.
Section 4.1.1.2	Added a new cohort, Cohort 12 (GEC) to be treated with budigalimab and mFOLFOX6	A checkpoint inhibitor (nivolumab) was approved in April 2021 for front line treatment of GEC with chemotherapy. Budigalimab, also a checkpoint inhibitor, would be expected to have activity in GEC when combined with chemotherapy. A recent review suggests that anti-PD-1 agents will be standard of care as first-line treatment of GEC (Smyth et al. 2021)
Section 4.1.1.2	Added new cohort, Cohort 11 (pancreatic carcinoma) to be treated with TTX-030 + gemcitabine + nab-paclitaxel. This cohort will include subjects enrolled in Study TTX-030-001 to enroll total number of subjects to N ≤23 response-evaluable subjects for the cohort.	To maximize recruitment efficiency for the program, Expansion Arm 4 from Study TTX-030-001 will continue enrollment into Study TTX-030-002 as both studies have overlapping study centers

Section #	Description of Change	Brief Rationale
Section 4.1.2	Added safety review after the first 6 patients have been enrolled into Cohort 9	To review early safety data during conduct of Cohort 9
Section 4.2	Added paragraph for the rationale for the discontinuation of Cohort 3 Arm A (TTX-030 + mFOLFOX6).	To provide the rationale for the discontinuation of Cohort 3 Arm A
Section 4.3.3, Section 4.3.4, Section 4.3.5	Added clause that dose modification for mFOLFOX6, docetaxel, nab-paclitaxel, and gemcitabine were to be implemented according to the current text "or to institutional guidelines."	To allow flexibility in dose modifications according to institutional guidelines
Section 5.1	Updated Inclusion Criterion #18 (new text in bold and deleted text in strikethrough): • No prior ~~chemotherapy~~ **treatment** for metastatic disease**, and no prior (neo-)adjuvant therapy** within 6 months of enrollment	To provide precise language regarding eligible prior treatment for study participants in Cohort 3
Section 5.1	Updated Inclusion Criterion #36 From: Ineligible for cisplatin and PD(L)-1 CPS ≥10 OR platinum ineligible regardless of PD(L)-1 status or received prior adjuvant platinum-based chemotherapy with disease recurrence >12 months since completion of therapy To: Subject must meet at least one of the following criteria: a) Subject is ineligible for any platinum-containing chemotherapy **OR** b) Subject experienced disease progression within 12 months of (neo-)adjuvant treatment with platinum-containing therapy	To provide precise language for the eligibility of the target patient population in Cohort 10 based on the pembrolizumab approved indication of locally advanced or metastatic UC
Section 5.1	Added a clause to Inclusion Criteria 7, 8b, and 10 for exceptions to the criteria with Medical Monitor approval.	To modify criteria for Cohort 10 with Medical Monitor approval.
Section 5.1, Section 5.2	Updated to include Cohort 11 and Cohort 12	To align with updated study design
Section 5.2	Reworded Exclusion Criterion #5	Clarification of which type of anticoagulation is allowed
Section 5.2	Reworded Exclusion Criterion #8e regarding uncontrolled diabetes	To define the appropriate population
Section 5.2	Removed "International normalized ratio >1.4 during screening" from Exclusion Criterion #15.	Covered in Inclusion Criterion #8e
Section 5.2 and Section 6.5.1	Updated to allow low-molecular-weight heparin, Factor Xa inhibitors, and low-dose aspirin. Removed clauses "for thrombosis" and "for deep vein thrombosis" from sentence.	Clarification
Section 6.1	• Clarified that IMPs and NIMPs administered in the study are summarized in Tables 6 and 7. • Updated Table 7 to include Cohort 11 and Cohort 12. • Clarified infusion duration of TTX-030 based on weight.	To align with updated study design and for clarification

Section #	Description of Change	Brief Rationale
	• Clarified route and duration for approved agents is per SOC.	
Section 6.3.1	Clarified sentence that Cohort 3 was randomized to add "prior to implementation of Protocol Amendment 4, Version 5.0 which discontinued Arm A".	To align with updated study design
Section 6.5.1	Removed clause "for deep vein thrombosis prophylaxis" from anticoagulation therapy paragraph.	To align with updated language in Exclusion Criterion #5.
Section 7.3, Section 7.3.1, Section 7.3.2	Added detail that subjects entering post-treatment follow up must have documented "radiographic" disease. Specified that study discontinuation or withdrawal other than documented disease progression must be "radiographic" disease progression. Added that efficacy follow ups will also continue until initiation of alternative treatment. Added that safety follow ups will also obtain survival status.	To add the requirement of radiographic disease progression and to further explain requirements and objectives of efficacy and safety follow ups.
Section 8.2.5	Added fibrinogen	To align with protocol changes
Section 8.3.5	Added sentence "For female subjects of reproductive potential that are receiving gemcitabine and nab-paclitaxel (Cohorts 9 and 11), subjects are advised to continue effective contraception for 180 days after the last dose of treatment.	To clarify duration of contraception for subjects using gemcitabine and nab-paclitaxel who may become pregnant.
Section 8.3.7	Removed tumor lysis syndrome as an AESI.	To omit tumor lysis syndrome as an AESI.
Section 8.3.8	Updated Medical Monitor	Change in personnel
Section 8.8	Updated language in tumor biopsy section	Clarification
Section 9.1	Updated sample size	To align with updated study design
Section 9.2	Removed "clinical progression" from description of Response-Evaluable Population.	Explanation of changes to definitions of population.
Section 9.3.1, Section 9.3.2	Added Expansion Cohort 12, Removed randomization from efficacy analyses.	Clarification and to reflect addition of Expansion Cohort.
Section 11.2, Appendix 2	Updated budigalimab (ABBV-181) toxicities management	To align with NCI CTCAE v5.0 toxicity grading and guidance

The rationale for prior amendments is included in Section 11.8.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
1L	first line
5-FU	5-fluorouracil
$A_{2a}R$	adenosine 2a receptor
ACTH	adrenocorticotropic hormone
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATP	adenosine triphosphate
CA 19-9	cancer-related antigen 19-9
CA 72-4	cancer-related antigen 72-4
CD	cluster of differentiation
CI	confidence interval
COVID-19	coronavirus disease 2019
CPS	combined positive score
CRC	colorectal cancer
CrCl	creatinine clearance
CT	computed tomography
CTLA-4	cytotoxic T-lymphocyte antigen-4
DLT	dose-limiting toxicity
dMMR	mismatch repair-deficient
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EOI	end of infusion
EU	European Union
FFPE	formalin-fixed paraffin-embedded
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GEC	gastroesophageal cancer
GI	gastrointestinal
GLP	Good Laboratory Practice
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
HNSTD	highest non-severely toxic dose
HPV	human papillomavirus

Abbreviation or Specialized Term	Definition
HR	hazard ratio
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFN	Interferon
IgG	immunoglobulin G
IHC	immunohistochemistry
IL	Interleukin
IMP	investigational medicinal product
INR	International Normalized Ratio
irAE	immune-related adverse event
IRB	Institutional Review Board
iRECIST	immunotherapy Response Evaluation Criteria in Solid Tumors
ISH	in situ hybridization
IV	intravenous(ly)
LH	luteinizing hormone
mCRPC	metastatic castration-resistant prostate cancer
MRI	magnetic resonance imaging
MSI-H	microsatellite instability-high
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIMP	non-investigational medicinal product
NOAEL	no-observed-adverse-effect level
NSCLC	non-small cell lung cancer
OCT	optimal cutting temperature
OPC	oropharyngeal cancer
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PCWG3	Prostate Cancer Working Group 3
PD	progressive disease
PD-1	programmed cell death-1
PD-L1	programmed cell death ligand-1
PD-L1	PD-1 or PD-L1
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PP	predictive probability
PSA	prostate-specific antigen
PT	prothrombin time
PTT	partial thromboplastin time

Abbreviation or Specialized Term	Definition
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
TEAE	treatment-emergent adverse events
Trishula	Trishula Therapeutics, Inc.
TSH	thyroid-stimulating hormone
UCC	Urothelial cell carcinoma
ULN	upper limit of normal
US	United States

1 PROTOCOL SUMMARY

1.1 Synopsis

Name of Sponsor/Company:
Trishula Therapeutics, Inc.

Name of Experimental Products:
TTX-030, Budigalimab (ABBV-181)

Name of Active Ingredient:
TTX-030, Budigalimab (ABBV-181)

TITLE
Phase 1/1b Study to Evaluate the Safety and Activity of TTX-030 (Anti-CD39) in Combination with Pembrolizumab or Budigalimab and/or Chemotherapy in Subjects with Advanced Solid Tumors

OBJECTIVES AND ENDPOINTS

Primary Objectives and Endpoints		
Type	**Objective**	**Endpoint**
Safety	• Safety Lead-in Cohorts: To assess the safety and tolerability of TTX-030 and budigalimab combination therapy in subjects with various advanced solid tumors • Expansion Cohorts: To assess the safety and tolerability of TTX-030 in combination with pembrolizumab or budigalimab and/or chemotherapy in subjects with selected advanced solid tumors	• Safety Lead-in Cohorts: The incidence of adverse events (AEs) and dose-limiting toxicities (DLTs), as well as changes from baseline in vital signs, clinical laboratory parameters, physical examination findings, Eastern Cooperative Oncology Group (ECOG) performance status, and electrocardiogram (ECG) results • Expansion Cohorts: The incidence of AEs, as well as changes from baseline in vital signs, clinical laboratory parameters, physical examination findings, ECOG performance status, and ECG results
Secondary Objectives and Endpoints		
Type	**Objective**	**Endpoint**
Efficacy	• Safety Lead-in Cohorts: To determine the preliminary clinical activity of TTX-030 and budigalimab combination therapy in subjects with various advanced solid tumors • Expansion Cohorts: To determine the clinical activity of TTX-030 in combination with pembrolizumab or budigalimab and/or chemotherapy in subjects with selected advanced solid tumors	• Objective response rate (ORR), best overall response (BOR), duration of response (DoR), disease control rate (DCR; defined as complete response [CR], partial response [PR], or stable disease [SD]), progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and immunotherapy RECIST (iRECIST), and overall survival (OS). For prostate adenocarcinoma, Prostate Cancer Working Group 3 (PCWG3) will be used.
Pharmaco-kinetics (PK)	• Safety Lead-in Cohorts: To describe the PK profiles of TTX-030 in subjects with various advanced solid tumors • Expansion Cohorts: To describe the PK profiles of TTX-030 in subjects with selected advanced solid tumors	• Serum concentration and PK parameters for TTX-030

Antidrug antibody (ADA)	• Safety Lead-in Cohorts: To describe the immunogenicity of TTX-030 in subjects with various advanced solid tumors • Expansion Cohorts: To describe the immunogenicity of TTX-030 in subjects with selected advanced solid tumors	• Number and percentage of subjects who develop ADA to TTX-030
Exploratory Objective and Endpoint		
Type	**Objective**	**Endpoint**
Pharmaco-dynamics	• To assess the effects of TTX-030 and budigalimab on pharmacodynamic biomarkers in peripheral blood and tumor tissue relating to mechanism of action, immune responses, and associated with PK/safety	Pharmacodynamic biomarkers and correlatives: • Exploratory pharmacodynamic biomarkers

OVERALL DESIGN

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

Safety Lead-in

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

Safety Lead-in Cohort 1 (28-Day Cycle)

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

In the Safety Lead-in Cohort 1, 6 subjects will receive the following combination regimen:

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

If ≥ 2 of the 6 evaluable subjects in Safety Lead-in Cohort 1 experience a DLT either De-escalation Cohort 1a or 1b could be explored based on the toxicity.

In Cohort 1a, 6 subjects will receive the following combination regimen:

- TTX-030 (40 mg/kg 7 days prior to Cycle 1 Day 1 followed by 20 mg/kg Q2W)
- Budigalimab (500 mg Q4W)
- mFOLFOX6 -- **Note:** A change to mFOLFOX6 (i.e., dose reduction or combination modification) may be permitted if the Cohort Review Committee determines that a potential DLT is a known chemotherapy-related toxicity. If known 5-FU or oxaliplatin toxicity occurs, the relevant drug should be dose reduced; 5-FU should be dose reduced prior to oxaliplatin.

If ≥2 of the 6 evaluable subjects in De-escalation Cohort 1a experience a DLT, based on the safety profile and preliminary antitumor activity, De-escalation Cohort 1b, with a doublet combination of TTX-030 and budigalimab or an alternative triplet combination of TTX-030, budigalimab, and mFOLFOX6, may be explored either after Cohort 1a or after the Safety Lead-in after review of the available safety and PK data. The proposed doublet and triplet combination regimens may include:

Doublet combination regimen:

- TTX-030 (40 mg/kg 7 days prior to Cycle 1 Day 1 followed by 20 mg/kg Q2W)
- Budigalimab (500 mg Q4W)

Triplet combination regimen:

- TTX-030 (30 mg/kg 7 days prior to Cycle 1 Day 1 followed by 20 mg/kg Q2W)
- Budigalimab (500 mg Q4W)
- mFOLFOX6 - **Note:** A change to mFOLFOX6 (i.e., dose reduction or combination modification) may be permitted if the Cohort Review Committee determines that a potential DLT is a known chemotherapy-related toxicity. If a known 5-FU or oxaliplatin toxicity occurs, the relevant drug should be dose reduced; 5-FU should be dose reduced prior to oxaliplatin.

Safety Lead-in Cohort 2 (21-Day Cycle)

In the Safety Lead-in Cohort 2, 6 subjects with metastatic castration-resistant prostate cancer (mCRPC) will receive the following combination regimen:

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

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

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

- TTX-030 (40 mg/kg 7 days prior to Cycle 1 Day 1 followed by 30 mg/kg Q3W)
- Budigalimab (375 mg Q3W)
- Docetaxel (60 mg/m^2 Q3W)

If ≥ 2 of the 6 evaluable subjects in De-escalation Cohort 2a experience a DLT, based on the safety profile and preliminary antitumor activity, Cohort 2b, with a doublet combination of TTX-030 and budigalimab or an alternative triplet combination of TTX-030, budigalimab, and docetaxel, may be explored either after Cohort 2a or after the Safety Lead-in after review of the safety and PK data. The proposed doublet and triplet combination regimens may include:

Doublet combination regimen:

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

Triplet combination regimen:

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

The study may be stopped early if any doses in the Safety Lead-in are considered unsafe. Conversely, the study may be stopped early for having sufficiently characterized the maximum tolerated dose if at least 6 subjects enrolled in each Safety Lead-in Cohort have completed the DLT evaluation period. After a safe dose level of TTX-030 combination therapy has been identified, a comparable fixed dose could be explored in a safety lead-in type design.

Expansion Phase

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

Expansion Cohorts 3 and 12

In Expansion Cohorts 3 and 12, a total of approximately 70 response-evaluable subjects (approximately 46 and 24 subjects, respectively) with human epidermal growth factor receptor 2 (HER2)-negative metastatic gastroesophageal cancer (GEC) will be enrolled (see Inclusion Criteria 16-18 and Exclusion 20-24). Study treatment will be administered at the doses and schedules identified in the Safety Lead-in.

- Cohort 3 Arm A: TTX-030 + mFOLFOX6 (n=6) [Note: Cohort enrollment discontinued in Protocol Amendment 4, Version 5.0]

- Cohort 3 Arm B: TTX-030 + budigalimab + mFOLFOX6 (n=40)
- Cohort 12: Budigalimab + mFOLFOX6 (n=24)

Expansion Cohorts 4 Through 11

In Expansion Cohorts 4, 6, 8, and 10, up to 23 response-evaluable subjects per cohort with selected advanced solid tumor types (listed below) will receive TTX-030 at the dose identified in the Safety Lead-in combination treatment that includes budigalimab Q3W in a 21-day cycle. In Expansion Cohorts 9 and 11, up to 23 response-evaluable subjects per cohort with unresectable or metastatic pancreatic adenocarcinoma will receive TTX-030 at the dose identified in the Safety Lead-in combination with chemotherapy at a Q2W in a 28-day cycle.

- Expansion Cohort 4: Metastatic colorectal cancer (CRC).
- Expansion Cohort 5: [Cohort removed under Amendment 3, Version 4.0].
- Expansion Cohort 6: Recurrent/metastatic head and neck squamous cell carcinoma (HNSCC). [Cohort enrollment discontinued under Amendment 3, Version 4.0].
- Expansion Cohort 7: [Cohort enrollment discontinued under Amendment 3, Version 4.0].
- Expansion Cohort 8: Advanced unresectable or metastatic adenocarcinoma of the stomach or gastroesophageal junction.
- Expansion Cohorts 9 and 11: Unresectable or metastatic previously untreated pancreatic adenocarcinoma.
- Expansion Cohort 10: Unresectable or metastatic urothelial cell carcinoma (UCC).

STUDY POPULATION

The Safety Lead-in and Expansion Phases of this study will enroll male or female subjects ≥ 18 years of age with evidence of measurable disease per RECIST v1.1 or iRECIST (except for mCRPC) and an ECOG performance status score of 0 or 1. Key disease-specific inclusion criteria are summarized by cohort below. The following cohorts may open or close dependent on Sponsor determination.

- **Safety Lead-in Cohort 1:** Unresectable or metastatic solid tumor malignancy
- **Safety Lead-in Cohort 2:** mCRPC with radiographic evidence of metastatic disease and disease progression (prostate-specific antigen progression per PCWG3 definition) on the recent prior systemic regimen and must have received at least 1 prior second-generation anti-androgen therapy (e.g., enzalutamide, abiraterone) approved for mCRPC and have not received docetaxel in the mCRPC setting and are eligible for docetaxel.
- **Expansion Cohorts 3 and 12:** Advanced unresectable or metastatic adenocarcinoma of the stomach or gastroesophageal junction with HER2-negative disease.
- **Expansion Cohort 4:** Metastatic CRC that is known to be microsatellite stable and has previously been treated with up to 3 prior systemic chemotherapy regimens for metastatic disease.
- **Expansion Cohort 5:** [This cohort was removed under Amendment 3, Version 4.0.]
- **Expansion Cohort 6:** Recurrent/metastatic HNSCC with progression on or after immune checkpoint inhibitors (anti-programmed cell death-1 [PD-1]/programmed cell death ligand-1 [PD-L1]) primary or secondary resistant. Subjects may have received up to 3 lines of prior systemic therapies for recurrent/metastatic disease. [Cohort enrollment discontinued under Amendment 3, Version 4.0.]
- **Expansion Cohort 7:** [Cohort enrollment discontinued under Amendment 3, Version 4.0.]
- **Expansion Cohort 8:** Advanced unresectable or metastatic adenocarcinoma of the stomach or gastroesophageal junction, previously treated with up to 3 prior systemic therapy regimens for metastatic disease, and anti-PD-L1 naïve.
- **Expansion Cohorts 9 and 11:** Unresectable or metastatic pancreatic adenocarcinoma naïve to any prior treatment for metastatic disease. Prior (neo-)adjuvant therapy is permitted if it was completed at least 6 months prior to study enrollment.
- **Expansion Cohort 10:** Unresectable or metastatic UCC.

TREATMENT GROUPS AND REGIMENS

Subjects in the Safety Lead-in and Expansion cohorts will receive TTX-030 in combination with pembrolizumab or budigalimab and/or chemotherapy as specified above in the Overall Design section.

Treatment with TTX-030 and/or budigalimab may continue for up to 24 months or until disease progression, intolerable toxicity, or death, whichever occurs first. If a subject discontinues any of the combination agents administered with TTX-030, then treatment with the remaining TTX-030-containing regimen may continue if it is well-tolerated.

STATISTICAL METHODS

Sample Size

Safety Lead-in

The planned sample size for the Safety Lead-in is a minimum of 6 subjects for each cohort. More subjects may be enrolled if lower doses are explored. Subjects are considered DLT evaluable if they complete the DLT evaluation period or experience a DLT during the DLT evaluation period. A subject not evaluable for DLT will be replaced with another subject at the same dose level.

Expansion Phase

The planned sample size is approximately 70 response-evaluable subjects for Expansion Cohorts 3 and 12 (approximately 46 and 24 subjects, respectively) and up to 115 subjects for Expansion Cohorts 4 through 11 (up to 23 subjects per cohort). [Cohorts 5 and 7 were removed under Amendment 3, Version 4.0; and enrollment into Cohort 6 was discontinued]. The sample size was selected to evaluate the safety profile and preliminarily efficacy. In Cohorts 4, 8, 9, and 10, an informal interim analysis will be performed when 14 subjects have been treated in an expansion cohort. Enrollment may continue during analysis. A second expansion of up to 40 subjects in select cohorts will be allowed based on review of safety, efficacy, and statistical considerations by the Sponsor and Cohort Review Committee. A subject who does not reach a first post-baseline scan (non-evaluable) will be replaced with another subject at the same dose level.

Safety

The safety analysis will be based on the All-Treated Population, which comprises all subjects who receive at least 1 dose or any partial dose of study treatment. The incidence of AEs (including DLTs for Safety Lead-in cohorts), and 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 treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAE severity/grade, and relationship to the investigational product(s). AEs will be graded according to the National Cancer Institute Common Terminology Criteria version 5.0 and coded using the Medical Dictionary for Regulatory Activities.

Efficacy

The efficacy analysis will be based on the Response-Evaluable Population, which comprises all subjects with measurable disease, as defined by tumor-specific response criteria, at baseline and with 1 of the following: 1) at least 1 on-treatment tumor assessment or 2) death.

Efficacy analyses for binary and time-to-event endpoints will be based on Investigator assessment according to RECIST v1.1 and iRECIST for all solid tumors, except mCRPC, which will be assessed according to the PCWG3 criteria. The following efficacy endpoints will be analyzed:

- **ORR**: Defined as the percentage of subjects with an unconfirmed/confirmed CR or unconfirmed/confirmed PR
- **BOR**: Defined as the best response observed at any of the subject's post-baseline assessments
- **DoR**: Defined as the time from first documentation of disease response (CR or PR) until first documentation of progressive disease (PD) or death from any cause, whichever occurs first
- **DCR**: Defined as the percentage of subjects with a BOR of CR, PR, or SD
- **PFS**: Measured from the start of investigational product treatment until first documentation of PD or death from any cause, whichever occurs first
- **OS**: Measured from the start of treatment until death due to any cause.

ORR and DCR will be estimated by the proportion of subjects with objective response and disease control, respectively, and their 80% confidence intervals will be estimated using the exact binomial method. Time-to-event endpoints (DoR, PFS, and OS) will be summarized using the Kaplan-Meier method.

Pharmacokinetics

The PK analysis will be based on the PK Population, which comprises all subjects who receive at least 1 dose of study treatment and have sufficient PK data. Serum concentrations of TTX-030 PK parameter values will be tabulated for each subject and each dose level. Summary statistics will be computed for each sampling time and each parameter.

Immunogenicity

The immunogenicity analysis will be based on the Immunogenicity Population, which comprises all subjects who receive at least 1 dose of study treatment and have available ADA data. Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of subjects who develop detectable anti-TTX-030 antibodies. The immunogenicity titer will be reported for samples confirmed positive for the presence of anti-TTX-030 antibodies.

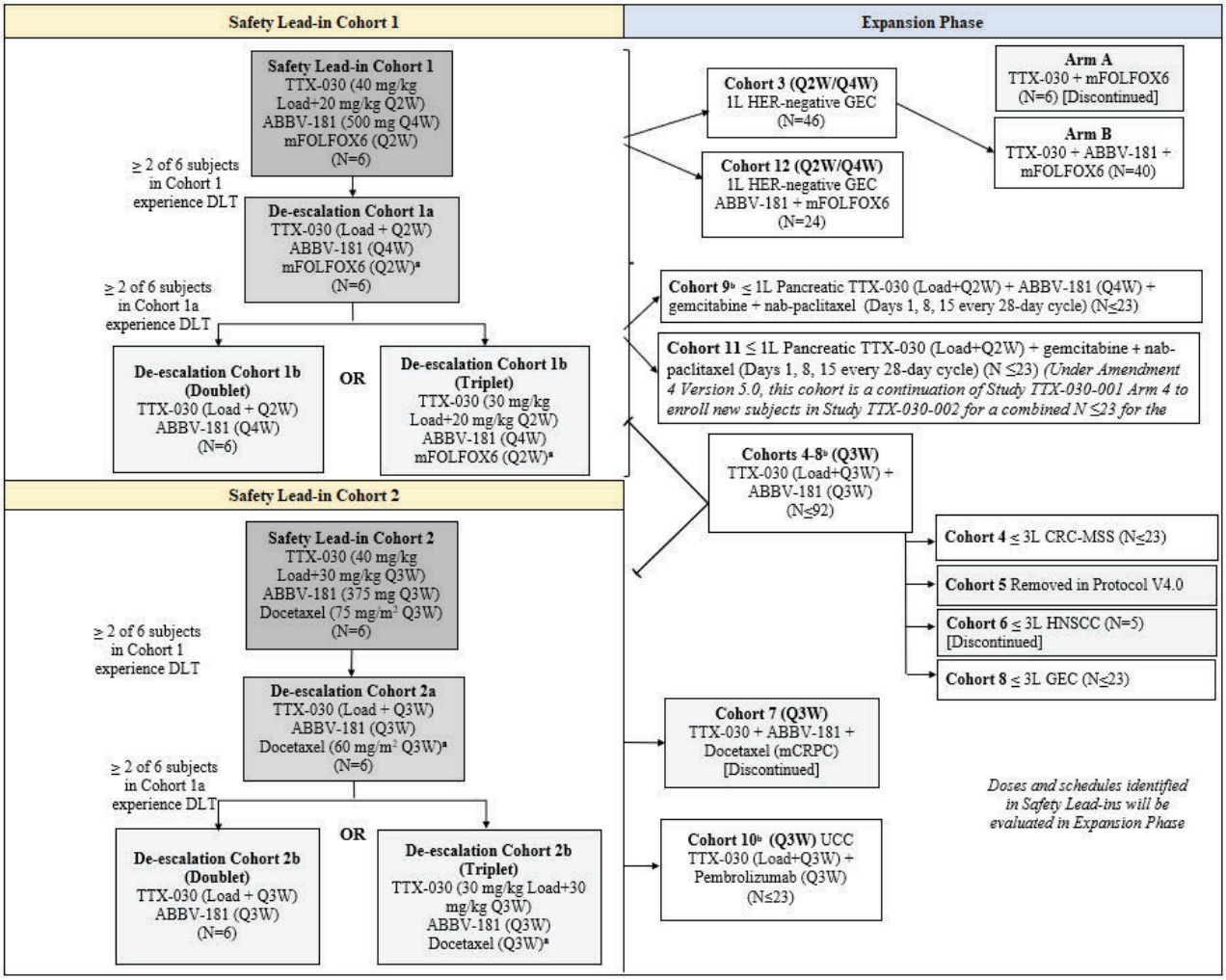
Biomarkers/Pharmacodynamics

The biomarker analyses are exploratory and will be based on the Biomarker/Pharmacodynamic Population, which comprises all subjects who receive at least 1 study treatment and have available biomarker data. Baseline and changes from baseline in biomarker measures will be summarized. Possible associations between changes in biomarker measures of interest and PK exposure will be explored. Possible associations 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.

1.2 Schema

The study schema is depicted in Figure 1.

Figure 1: Study Schema



1L=first line; 3L=third line; budigalimab=ABBV-181; CRC-MSS=colorectal cancer-microsatellite stable; DLT=dose-limiting toxicity; GEC=gastroesophageal cancer; HER2=human epidermal growth factor receptor 2; HNSCC=head and neck squamous cell carcinoma; mCRPC=metastatic castration-resistant prostate cancer;
Q2W=every 2 weeks; Q3W=every 3 weeks; Q4W=every 4 weeks; UCC=urothelial call carcinoma.

[a] A dose reduction of mFOLFOX6 or docetaxel may be permitted if the Cohort Review Committee determines that a potential DLT is a known chemotherapy-related toxicity.

[b] Expansion Cohorts 4, 8, 9, 10, and 11 may start when either Safety Lead-in Cohort 1 or 2 completes the DLT-evaluation period.

Notes:

- Expansion of up to 40 subjects in select cohorts will be allowed based on review of safety, efficacy, and statistical considerations by the Sponsor and Cohort Review Committee.
- For Cohorts 9 and 11, subjects will be assigned to a cohort at the time of enrollment by the Sponsor.
- The targeted enrollment number for subjects in the expansion cohorts represents the number of response-evaluable subjects.

1.3 Schedule of Activities

1.3.1 Screening, Baseline, and Pre-C1D1 (Loading Dose) Assessments

Assessments to be performed at screening, baseline, and loading dose visits are shown in Table 1 for all cohorts.

Table 1: Schedule of Activities at Screening, Baseline, and Loading Dose Visits

Assessment	Pretreatment		Pre-C1D1
	Screening (up to 28 days prior to loading dose/first dose)	Baseline[a] (up to 3 days prior to loading dose/first dose)	Loading Dose[a] (Day -7)
Informed consent	X		
Eligibility criteria	X		
Demographics	X		
Medical history and prior anticancer treatments	X		
Confirmation of diagnosis (tumor history)	X		
Cohort assignment[a]		X	
Physical examination	X	X	
Height	X		
Vital signs (temperature, HR, BP, weight)	X	X	
ECOG performance status	X		
Triplicate 12-lead ECG	X		
MUGA/ECHO[b]	X		
HbA1c[c]	X		
Serum chemistry and hematology	X	X	
Thyroid function tests[c]		X	
Pituitary function tests		X	
Coagulation profile (PT/INR, PTT, fibrinogen)	X	X	
Urinalysis	X	X	
Hepatitis serology tests (HBsAg, anti-HBc, and anti-HCV)[d]	X		
HPV test for HNSCC (Expansion Cohort 6 only if HPV status is not known prior to screening)	X		
Pregnancy test[e]	X	X	
Contraception check	X	X	
Tumor assessment with contrast (CT/MRI, bone scans)[f]	X		
Serum tumor-associated marker(s) (e.g., CEA, PSA, CA 19-9, CA 72-4)	X		
PK blood samples[g]			X (pre & post infusion)
ADA blood samples[h]		X	
Pharmacodynamic and correlative blood samples[h]		X	X
Pharmacodynamics – plasma (Streck tubes)[h]		X	
Tumor biopsy[i]	X		
TTX-030 only infusion (not applicable to Cohort 12)[j]			X
Concomitant medications[k]	X	X	X
Adverse events[l]	X	X	X

ADA=antidrug antibody; AESI=adverse event of special interest; anti-HBc=hepatitis B core antibody; BP=blood pressure; C=cycle; CA 19-9=cancer-related antigen 19-9; CA 72-4=cancer-related antigen 72-4; CEA=carcinoembryonic antigen; COVID-19=coronavirus disease 2019; CPS=combined positive score; CT=computed tomography; D=day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOI=end of infusion; FSH=follicle-stimulating hormone;

HbsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HbA1c=hemoglobin A1c; HNSCC=head and neck squamous cell carcinoma; HPV=human papillomavirus; HR=heart rate; INR=international normalized ratio; mCRPC=metastatic castration-resistant prostate cancer; MRI=magnetic resonance imaging; MUGA/ECHO=multigated acquisition/echocardiogram; PCR=polymerase chain reaction; PD-L1=programmed cell death ligand 1; PET=positron emission tomography; PK=pharmacokinetics; PSA=prostate-specific antigen; PT=prothrombin time; PTT=partial thromboplastin time; SAE=serious adverse event; TSH=thyroid-stimulating hormone.

[a] Baseline assessments may not need to be repeated if they were part of the screening visit and occurred within 3 days of the loading dose/first dose. Cohort assignment is to occur within 3 days before the start of loading dose/first dose. Baseline assessments can be performed pre-dose on pre-C1D1 visit (cohorts with loading dose). **For Cohort 12,** not TTX-030 is administered. As such, the loading dose visit is not applicable; baseline assessments can be performed pre-dose on C1D1 visit (Cohort 12).

[b] MUGA/ECHO is required for subjects with history of congestive heart failure.

[c] HbA1c and thyroid function tests (TSH only) are to be performed at Baseline and then every 3 months. Free T3, free T4, and thyroid antibody tests are to be performed as reflex for abnormal TSH.

[d] 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 enrollment.

[e] 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.

[f] CT/MRI scans of the chest, abdomen, and pelvis are required for all subjects. HNSCC subjects must have CT/MRI scans of the head, neck, and chest. Tumor assessments will include all known or suspected disease sites. Anatomic regions included in the CT/MRI scans should be per disease history and clinical symptoms (repeat the same CT/MRI series for all post-treatment tumor assessments as completed at Screening). If subjects is allergic to contrast agents for imaging, CT without contrast, MRI, or PET scans will be allowed. The imaging modality and anatomic regions used must be uniform during study participation. Brain scans and bone scans will be performed at screening if disease is suspected and on study as appropriate to follow disease. See Section 8.1.

[g] Post-dose PK sample collection should occur 45 (±15) min after the EOI of TTX-030. If using the same infusion filter line for PK draw, flushing is required.

[h] ADA, pharmacodynamic, and biomarker blood draws should occur at the same time as PK blood draw and tumor biopsy when applicable. When pre-dose PK samples are collected, collect ADA, pharmacodynamic, and biomarker samples with the pre-dose PK.

[i] Eligible subjects will be required to have a site of disease that is safely accessible for screening and on-study biopsy (paired biopsy). Archival FFPE tumor tissue may be used as baseline biopsy sample if it was obtained within 90 days of the loading dose/first dose, and if the subject has not had any intervening treatment. If the biopsy procedure is considered clinically contraindicated, discuss with the Medical Monitor. Please see Section 8.8 and the laboratory manual for additional details regarding biopsy requirements and collection.

[j] Loading dose of TTX-030 monotherapy will be administered per IMP Manual. If using the same infusion filter line for PK draw, flushing is required.

[k] Concomitant medication information is to be collected from 30 days prior to Screening through 30 days after the last dose of study treatment.

[l] Adverse events (e.g., including COVID-19 symptoms) and AESIs are to be collected from the time subject provides written informed consent through 90 days after the last administration of study treatment or until initiation of a new systemic anticancer therapy, whichever occurs first. Positive COVID-19 test results will be submitted as an SAE.

1.3.2 Assessments During Treatment

Assessments to be performed during treatment are presented for Safety Lead-in Cohort 1 and Expansion Cohorts 3, 9, 11, and 12 in Table 2 and for Safety Lead-in Cohort 2 and Expansion Cohorts 4, 6, 8, and 10 in Table 3.

Table 2: Schedule of Activities During Treatment for Safety Lead-in Cohort 1 and Expansion Cohorts 3, 9, 11, and 12

Assessment	Cycle 1			Cycle 2			Cycle 3			Cycle 4+	
	D1	D8	D15 (±1)	D29 (+2)	D36 (±2)	D43 (±2)	D57 (±2)	D64 (±2)	D71 (±2)	D85 (±2) & Q28D Thereafter	D99 (±2) & Subsequent CXD15
	C1D1	C1D8	C1D15	C2D1	C2D8 Cohorts 9 and 11[i]	C2D15	C3D1	C3D8 & Subsequent CXD8[i]	C3D15	CXD1[f,g,h,i]	CXD15[f,h,i]
Physical examination[a]				X			X			X	
Symptom-directed examination	X	X	X		X	X		X	X		X
Vital signs (temperature, HR, BP, weight)[a]	X	X	X	X	X	X	X	X	X	X	X
ECOG performance status	X			X			X			X	
Triplicate 12-lead ECG[b]	X			X			X			X	
Serum chemistry and hematology[a]	X	X	X	X	X	X	X	X	X	X	X
HbA1c										X[c]	
Thyroid function tests[c]							X			X[c]	
Coagulation profile (PT/INR, PTT)	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X			X			X			X	
Pregnancy test[d]	X			X			X			X	
Contraception check	X	X	X	X	X	X	X	X	X	X	X
Tumor assessment with contrast (CT/MRI, bone scans)[e]							X (-7 days)			Q8W (-7 days) starting on C5D1	
Serum tumor-associated markers (e.g., CEA, PSA, CA 19-9, CA 72-4)				X			X			X	
TTX-030 Q2W[f] (not for Cohort 12)	X		X	X		X	X		X	X	X
Budigalimab Q4W (Cohorts 1, 3 Arm B, 9, or 12)[g]	X			X			X			X	
mFOLFOX6 Q2W (Cohorts 1, 3, and 12)[h]	X		X	X		X	X		X	X	X

Assessment	Cycle 1			Cycle 2			Cycle 3			Cycle 4+	
	D1	D8	D15 (±1)	D29 (+2)	D36 (±2)	D43 (±2)	D57 (±2)	D64 (±2)	D71 (±2)	D85 (±2) & Q28D Thereafter	D99 (±2) & Subsequent CXD15
	C1D1	C1D8	C1D15	C2D1	C2D8 Cohorts 9 and 11[i]	C2D15	C3D1	C3D8 & Subsequent CXD8[i]	C3D15	CXD1[f,g,h,i]	CXD15[f,h,i]
Gemcitabine+nab-paclitaxel (Cohorts 9 and 11)[i]	X	X	X	X	X	X	X	X	X	X	X
PK blood sample[j]	X (pre & post infusion)	X (pre)	X (pre & post infusion)	X (pre & post infusion)			X (pre & post infusion)			X (pre [all] & post infusion [C6D1])	
ADA blood sample[k]	X		X	X			X			X	
Pharmacodynamic and correlative blood samples[k]	X	X	X	X		X	X			X	
Pharmacodynamics – plasma (Streck tubes)[k]				X			X				
Tumor biopsy[l]				X (-7 days)							
Concomitant medications[m]	X	X	X	X	X	X	X	X	X	X	X
Adverse events[n]	X	X	X	X	X	X	X	X	X	X	X

ADA=antidrug antibody; AESI=adverse event of special interest; BP=blood pressure; C=Cycle; CA 19-9=cancer-related antigen 19-9; CA 72-4=cancer-related antigen 72-4; CEA=carcinoembryonic antigen; COVID-19=coronavirus disease 2019; CT=computed tomography; D=Day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; FSH=follicle-stimulating hormone; HbA1c=hemoglobin A1c; HNSCC=head and neck squamous cell carcinoma; HR=heart rate; INR=international normalized ratio; MRI=magnetic resonance imaging; PD=pharmacodynamic; PET=positron emission tomography; PK=pharmacokinetics; PSA=prostate-specific antigen; PT=prothrombin time; PTT=partial thromboplastin time; Q28D=every 28 days; Q2W=every 2 weeks; Q4W=every 4 weeks; Q8W=every 8 weeks; SAE=serious adverse event; TSH=thyroid-stimulating hormone.

[a] Laboratory tests (including pregnancy testing), physical exam, and weight do not need to be repeated if they were performed within 3 days prior to dosing.
[b] Standard 12-lead ECG (collect before PK draw): at each timepoint, 3 consecutive 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.
[c] HbA1c and thyroid function tests (TSH only) are to be performed every 3 months. Free T3, free T4, and thyroid antibody tests are to be performed as reflex for abnormal TSH.
[d] Serum pregnancy 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.
[e] CT/MRI scans of the chest, abdomen, and pelvis are required for all subjects. HNSCC subjects must have CT/MRI scans of the head, neck, and chest. Tumor assessments will include all known or suspected disease sites. Anatomic regions included in the CT/MRI scans should be per disease history and clinical symptoms (repeat the same CT/MRI series for all post-treatment tumor assessments as completed at Screening). If subject is allergic to contrast agents for imaging, CT without contrast, MRI, or PET scans will be allowed. The imaging modality and anatomic regions used must be uniform during study participation. Brain scans and bone scans will be performed at screening if disease is suspected and on

study as appropriate to follow disease. Tumor assessment should be repeated at the end of treatment visit if more than 6 weeks (±7 days) have passed since the last evaluation. See also Section 8.1.

[f] **For Cohorts 1, 3 Arm B, and 9**: TTX-030 (Q2W) will be administered at least 60 minutes prior to budigalimab (Q4W); **for Cohort 3 Arm A and Cohort 11**: TTX-030 (Q2W) will be administered at least 60 minutes prior to mFOLFOX6 chemotherapy (Q2W). A minimum of 60 minutes wait time in between infusion is required to monitor for potential infusion-related reactions prior to the administration of another drug.

[g] **For Cohorts 1, 3 Arm B, and 9**: Budigalimab (Q4W) will be administered at least 60 minutes after completion of the TTX-030 infusion and the collection of the PK EOI sample. Infuse budigalimab over at least 60 minutes or longer, until bag is empty to complete administration of full dose. A minimum of 60 minutes wait time in between infusions is required to monitor for potential infusion-related reactions prior to the administration of another drug.

[h] **For Cohorts 1 and 3 Arm B:** mFOLFOX6 (Q2W) (oxaliplatin 85 mg/m^2 IV with leucovorin 400 mg/m2 IV over 2 hours plus 5-FU 400 mg/m2 IV bolus and 2400 mg/m2 continuous infusion over 46 hours) will be administered at least 60 minutes after completion of the budigalimab infusion; for Cohort 12: mFOLFOX6 will be administered at least 60 minutes after completion of the budigalimab infusion. Cycle 4 and beyond also require a dosing visit at Day 15.

[i] **For Cohorts 9 and 11** - Gemcitabine 1000 mg/m^2 + nab-paclitaxel 125 mg/m^2 (Days 1, 8, and 15 each 28-day cycle) will be administered after completion of the infusion of budigalimab (Cohort 9) or TTX-030 (Cohort 11). Cycle X Day 8 visits/procedures beyond Cycle 1 only apply to Cohorts 9 and 11. A minimum of 60 minutes wait time after budigalimab infusion is required to monitor for potential infusion-related reactions prior to the administration of another drug.

[j] Post-dose PK sample collection should occur 45 (±15) min after the EOI of TTX-030. If using the same infusion filter line for PK draw, flushing is required.

[k] ADA, PD, and biomarker blood draws should occur at the same time as PK blood draw and tumor biopsy when applicable. When pre-dose PKs are collected, collect ADA, PD, and biomarker samples with the pre-dose PK.

[l] Enrolled subjects will be required to have a site of disease that is safely accessible for screening and on-study biopsy (paired biopsy). Archival FFPE tumor tissue may be used as baseline biopsy sample if it was obtained within 90 days of the loading dose/first dose, and if the subject has not had any intervening treatment. If the biopsy procedure is considered clinically contraindicated, discuss with the Medical Monitor. Please see Section 8.8 and the laboratory manual for additional details regarding biopsy requirements and collection.

[m] Concomitant medication information is to be collected from 30 days prior to Screening through 30 days after the last dose of study treatment.

[n] Adverse events (e.g., including COVID-19 symptoms) and AESIs are to be collected from the time subject provides written informed consent through 90 days after the last administration of study treatment or until initiation of a new systemic anticancer therapy, whichever occurs first. A positive COVID-19 test result will be submitted as an SAE.

Table 3: Schedule of Activities During Treatment for Safety Lead-in Cohort 2 and Expansion Cohorts 4, 6, 8, and 10

Assessment	Cycle 1		Cycle 2	Cycle 3	Cycle 4+
	D1	D8	D22 (±2)	D43 (±2)	D64 (±2) & Q21D Thereafter
	C1D1	C1D8	C2D1	C3D1	CXD1
Physical examination[a]			X	X	X
Symptom-directed examination	X	X			
Vital signs (temperature, HR, BP, weight)	X	X	X	X	X
ECOG performance status	X		X	X	X
Triplicate 12-lead ECG[b]	X		X	X	X
Serum chemistry and hematology[a]	X	X	X	X	X
HbA1c					X[c]
Thyroid function tests[c]					X
Coagulation profile (PT/INR, PTT)	X	X	X	X	X
Urinalysis	X		X	X	X
Pregnancy test[d]	X		X	X	X
Contraception check	X	X	X	X	X
Tumor assessment with contrast[e] (CT/MRI, bone scans)					Q9W (−7 days) starting on C4D1
Serum tumor-associated markers (e.g., CEA, PSA, CA 19-9, CA 72-4)			X	X	X
TTX-030 Q3W[f]	X		X	X	X
Budigalimab (ABBV-181) Q3W[g] (Cohorts 2, 4, 6, or 8 only)	X		X	X	X
Docetaxel Q3W (Cohort 2)[h]	X		X	X	X
Pembrolizumab Q3W (Cohort 10)[i]	X		X	X	X
PK blood sample[j]	X (pre & post infusion)	X (pre)	X (pre & post infusion)	X (pre & post infusion)	X (pre [all] & post infusion [C6D1])
ADA blood sample	X		X	X	X
Pharmacodynamic and correlative blood samples[k]	X	X	X	X	X
Pharmacodynamics – plasma (Streck tubes)[k]			X	X	
Tumor biopsy[l]			X (-7 days)		
Concomitant medications[m]	X	X	X	X	X

Assessment	Cycle 1		Cycle 2	Cycle 3	Cycle 4+
	D1	D8	D22 (±2)	D43 (±2)	D64 (±2) & Q21D Thereafter
	C1D1	C1D8	C2D1	C3D1	CXD1
Adverse events[n]	X	X	X	X	X

ADA=antidrug antibody; AESI=adverse event of special interest; BP=blood pressure; C=Cycle; CA 19-9=cancer-related antigen 19-9; CA 72-4=cancer-related antigen 72-4; CEA=carcinoembryonic antigen; COVID-19=coronavirus disease 2019; CT=computed tomography; D=Day; ECOG=Eastern Cooperative Oncology Group; EOI=end of infusion; FSH=follicle-stimulating hormone; HbA1c=hemoglobin A1c; HNSCC=head and neck squamous cell carcinoma; HR=heart rate; INR=international normalized ratio; mCRPC=metastatic castration-resistant prostate cancer; MRI=magnetic resonance imaging; PD=pharmacodynamic; PET=positron emission tomography; PK=pharmacokinetics; PSA=prostate-specific antigen; PT=prothrombin time; PTT=partial thromboplastin time; Q3W=every 3 weeks; Q9W=every 9 weeks; Q21D=every 21 days; SAE=serious adverse event.

[a] Laboratory tests (including pregnancy testing), physical exam, and weight do not need to be repeated if they were performed within 3 days prior to dosing.
[b] Standard 12-lead ECG (collect before PK draw): at each timepoint, 3 consecutive 12-lead ECGs will be performed approximately 2 minutes (or 1 minute, if applicable) apart to determine mean QTc interval.
[c] HbA1c and thyroid function tests (TSH only) are to be performed every 3 months. Free T3, free T4, and thyroid antibody tests are to be performed as reflex for abnormal TSH.
[d] 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.
[e] CT/MRI scans of the chest, abdomen, and pelvis are required for all subjects. HNSCC subjects must have CT/MRI scans of the head, neck, and chest. Tumor assessments will include all known or suspected disease sites. Anatomic regions included in the CT/MRI scans should be per disease history and clinical symptoms (repeat the same CT/MRI series for all post-treatment tumor assessments as completed at Screening). If subject is allergic to contrast agents for imaging, CT without contrast, MRI or PET scans will be allowed. The imaging modality and anatomic regions used must be uniform during study participation. Brain scans and bone scans will be performed at screening if disease is suspected and on study as appropriate to follow disease. Tumor assessment should be repeated at the end of treatment visit if more than 6 weeks (±7 days) have passed since the last evaluation. See also Section 8.1.
[f] TTX-030 (Q3W) will be administered at least 60 minutes prior to budigalimab or pembrolizumab. A minimum of 60 minutes wait time in between infusion is required to monitor for potential infusion-related reactions prior to the administration of another drug.
[g] **For Cohorts 2, 4, and 8:** Budigalimab (Q3W) will be administered at least 60 minutes after completion of the TTX-030 infusion and the collection of the PK EOI sample. Infuse budigalimab over at least 60 minutes or longer, until bag is empty to complete administration of a full dose. A minimum of 60 minutes wait time in between infusions is required to monitor for potential infusion-related reactions prior to the administration of another drug.
[h] **For Cohort 2:** Docetaxel (Q3W) will be administered at least 60 minutes after completion of the budigalimab infusion.
[i] **For Cohort 10:** Pembrolizumab (Q3W) will be administered at least 60 minutes after completion of the TTX-030 infusion.
[j] Post-dose PK sample collection should occur 45 (±15) min after the EOI of TTX-030. If using the same infusion filter line for PK draw, flushing is required.
[k] ADA, PD, and biomarker blood draws should occur at the same time as PK blood draw and tumor biopsy when applicable. When pre-dose PKs are collected, collect ADA, PD, and biomarker samples with the pre-dose PK.
[l] Enrolled subjects will be required to have a site of disease that is safely accessible for screening and on-study biopsy (paired biopsy). Archival FFPE tumor tissue may be used as baseline biopsy sample if it was obtained within 90 days of the loading dose/first dose, and if the subject has not had any intervening treatment. If the biopsy procedure is considered clinically contraindicated, discuss with the Medical Monitor. Please see Section 8.8 and the laboratory manual for additional details regarding biopsy requirements and collection.
[m] Concomitant medication information is to be collected from 30 days from Screening through 30 days after the last dose of study treatment.
[n] Adverse events (e.g., including COVID-19 symptoms) and AESIs are to be collected from the time subject provides written informed consent through 90 days after the last administration of study treatment or until initiation of a new systemic anticancer therapy, whichever occurs first. A positive COVID-19 test result will be submitted as an SAE.

1.3.3 End-of-Treatment and Follow-Up Assessments

Assessments to be performed at end of treatment and during follow-up are shown in Table 4 for all cohorts.

Table 4: Schedule of Activities at End of Treatment and During Follow-Up

Assessment	EOT	Follow-Up		
	30 (±9) Days After Last Dose	Efficacy Follow-up[a]	Safety Contact 60 & 90 (±7) Days After Last Dose	Survival Contact 180 (±15) Days After Last Dose
Physical examination	X	X		
Vital signs (temperature, HR, BP, weight)	X			
ECOG performance status	X			
Triplicate 12-lead ECGs	X			
Serum chemistry and hematology[b]	X			
Coagulation profile (PT/INR, PTT)	X			
Pregnancy test	X			
Contraception check[c]	X	X	X	X[g]
Tumor assessment with contrast (CT/MRI, bone scans)[d]	X	X[a]		
Serum tumor-associated markers (e.g., CEA, PSA, CA 125, CA 19-9, CA 72-4)	X	X[a]		
PK blood samples	X			
ADA blood samples[e]	X			
Pharmacodynamic and correlative blood samples[e]	X			
Pharmacodynamics – plasma (Streck tubes)[e]	X			
Concomitant medications[f]	X			
Adverse events[g]	X	X	X	
Post-treatment anticancer therapy	X	X	X	X
Follow-up contact	X	X	X	X

ADA=antidrug antibody; AESI=adverse event of special interest; BP=blood pressure; CA 19-9=cancer-related antigen 19-9; CA 72-4=cancer-related antigen 72-4; CEA=carcinoembryonic antigen; COVID-19=coronavirus disease 2019; CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; HNSCC=head and neck squamous cell carcinoma; HR=heart rate; INR=international normalized ratio; mCRPC=metastatic castration-resistant prostate cancer; MRI=magnetic resonance imaging; PD=pharmacodynamic; PET=positron emission tomography; PK=pharmacokinetics; PSA=prostate-specific antigen; PT=prothrombin time; PTT=partial thromboplastin time; SAE=serious adverse event.

[a] Subjects who discontinue treatment for reasons other than documented radiographic disease progression will undergo tumor assessments and serum tumor-associated marker evaluation (every 8 weeks [28-day cycle] or 9 weeks [21-day cycle]) until disease progression or until the subject comes off study or starts alternative anticancer treatment.

[b] EOT laboratory assessments do not need to be repeated if laboratory assessments were collected on study within the past 5 days.

[c] Contraception check is required until 150 days after last administration of study treatment and until 180 days after the last dose of gemcitabine/nab-paclitaxel.

[d] CT/MRI scans of the chest, abdomen, and pelvis are required for all subjects. HNSCC subjects must have CT/MRI scans of the head, neck, and chest. Tumor assessments will include all known or suspected disease sites. Anatomic regions included in the CT/MRI scans should be per disease history and clinical symptoms (repeat the same CT/MRI series for all post-treatment tumor assessments as completed at Screening). If subject is allergic to contrast agents for imaging, CT without contrast, MRI, or PET scans will be allowed. The imaging modality and anatomic regions used must be uniform during study participation. Brain scans and bone scans will be performed at screening if disease is suspected and on study as appropriate to follow disease. Tumor assessment should be repeated at the end-of-treatment visit if more than 6 weeks (±7 days) have passed since the last evaluation. See also Section 8.1. An independent radiology read may be performed in select subjects/cohorts.

[e] ADA, PD, and biomarker blood draws should occur at the same time as the PK blood draw.

[f] Concomitant medication information is to be collected from 30 days from Screening through 30 days after the last dose of study treatment.

[g] Adverse events (e.g., including COVID-19 symptoms) and AESIs are to be collected from the time subject provides written informed consent through 90 days after the last administration of study treatment or until initiation of a new systemic anticancer therapy, whichever occurs first. A positive COVID-19 test result will be submitted as an SAE.

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 pembrolizumab or budigalimab (ABBV-181) and/or chemotherapy, in advanced solid tumor types. The rationale for these combinations is provided in Section 2.2.5, Section 2.2.8, Section 2.2.10, and Section 2.2.13.

2.2 Background

Immune checkpoint inhibitors have revolutionized the cancer treatment paradigm. These agents modulate the tumor microenvironment or other aspects of the immune system to overcome the immune suppression that a tumor elicits on the host immune system. Anti-PD-1/programmed cell death ligand-1 (PD-L1) agents such as nivolumab (OPDIVO PI, 2021), pembrolizumab (KEYTRUDA PI, 2020), cemiplimab (LIBTAYO PI, 2019), atezolizumab (TECENTRIQ PI, 2019), avelumab (BAVENCIO PI, 2019), and durvalumab (IMFINZI PI, 2018) and the anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) agent ipilimumab (YERVOY PI, 2019), all of which target immunosuppressive pathways, have been approved and have proven to be beneficial in numerous tumor types.

Research over the past decade has led to the discovery of several new immunomodulatory pathways (Marin-Acevedo et al, 2018; Le Mercier et al, 2015). Among them, the adenosine pathway has emerged as one of the most promising targets in immuno-oncology. Adenosine is an immunosuppressive metabolite produced at high levels within the tumor microenvironment. It is mainly generated extracellularly through sequential dephosphorylation of adenosine triphosphate (ATP) by the ectonucleotidases CD39 and CD73. Reportedly, both CD39 and CD73 are elevated in blood neoplasias, such as leukemia and lymphoma, as well as in multiple solid tumor types (Bastid et al, 2013). In solid tumors, ATP is abundantly released in the extracellular space, achieving concentrations more than a thousand times higher than in healthy tissues. This is primarily due to cell death in the tumor core, metabolic or hypoxic stress, and pro-inflammatory signals that stimulate active export of ATP (Pellegatti et al, 2008; Di Virgilio et al, 2016). In addition, chemotherapy-induced immunogenic cell death is in part mediated by the release of extracellular ATP (Martins et al, 2009). Tumors are proficient at converting ATP into adenosine via CD39 and CD73 on malignant cells, regulatory immune cells, and the vasculature. These ectonucleotidases modulate purinergic signaling by scavenging mainly pro-inflammatory ATP and generating immunosuppressive adenosine (Allard et al, 2017).

CD39, the main rate-limiting enzyme in the adenosine cascade, has an important role in tumor progression. Blockade of CD39 enzymatic activity may stimulate antitumor immunity across a wide range of tumors by preventing the production of immunosuppressive adenosine and by promoting the accumulation of ATP in the tumor microenvironment. CD39 can be viewed as an immunological switch that shifts ATP-driven pro-inflammatory immune cell activity toward an anti-inflammatory state mediated by adenosine and is, therefore, a unique therapeutic target for oncology indications (Antonioli et al, 2014; Cai et al, 2016).

2.2.1 Background on Individual Tumor Types

This study will be conducted in adults with advanced solid tumors. The tumor types to be evaluated in the Expansion Phase are described below.

2.2.1.1 Human Epidermal Growth Factor Receptor 2-negative Gastroesophageal Cancer

Gastroesophageal cancer (GEC) is the fifth most frequently diagnosed cancer and the third leading cause of cancer-related death worldwide (Bray et al, 2018). In 2018, more than 1.6 million new GEC cases and approximately 1.3 million associated deaths were estimated to occur. In the United States (US), an estimated 45,000 new cases of GEC will be diagnosed in 2019, and there will be approximately 27,000 GEC-related deaths (Siegel et al, 2020). GEC remains difficult to cure because most patients present with advanced disease. The prognosis of advanced GEC is poor, with a 5-year overall survival (OS) rate estimated around 5% to 20% (Wagner et al, 2017).

Treatment of advanced/metastatic GEC is based on human-epidermal growth factor receptor 2 (HER2) status (NCCN Guidelines Gastric Cancer, 2019). However, unlike in breast cancer, the prognostic significance of HER2 status in GEC is unclear. While further research is needed to assess the prognostic significance of HER2 status in GEC, the addition of HER2 monoclonal antibodies to chemotherapy regimens has proved to be a promising treatment option for patients with HER2-positive metastatic disease, which accounts for 12% to 23% of GEC. For patients with HER2-negative GEC, chemotherapy is the standard first-line treatment for advanced disease. Currently, a fluoropyrimidine (fluorouracil or capecitabine) combined with a platinum (oxaliplatin or cisplatin) is the mainstay of chemotherapy (NCCN Guidelines Gastric Cancer, 2019). A Phase 3 trial conducted by the German Study Group compared treatment with fluorouracil plus cisplatin to fluorouracil plus oxaliplatin (FOLFOX) in 220 patients with previously untreated advanced adenocarcinoma of the stomach or esophagogastric junction cancer (Al-Batran et al, 2008). Results showed that FOLFOX was associated with significantly less toxicity and a trend toward improved median progression-free survival (PFS), compared with fluorouracil plus cisplatin (5.8 vs 3.9 months; p=0.77). There was no significant difference in median OS between the 2 groups (10.7 vs 8.8 months, respectively). In patients >65 years of age, FOLFOX resulted in superior response rates (41.3 vs 16.7%, respectively; p=0.12), time to treatment failure (5.4 vs 2.3 months; p <0.001), PFS (6.0 vs 3.1 months; p=0.029), and OS (13.9 vs 7.2 months), compared with fluorouracil plus cisplatin. FOLFOX offers reduced toxicity and similar efficacy compared with fluorouracil plus cisplatin and may also be associated with improved efficacy in older adult patients. The safety and efficacy of FOLFOX have also been demonstrated in other studies (Enzinger et al, 2016; Louvet et al, 2002; Al-Batran et al, 2004). Other recommended regimens for first-line therapy include capecitabine plus cisplatin; combination of docetaxel, cisplatin, and fluorouracil; irinotecan plus fluorouracil (FOLFIRI); paclitaxel with either cisplatin or carboplatin; docetaxel plus cisplatin; or single-agent fluoropyrimidine (fluorouracil or capecitabine), docetaxel, or paclitaxel (NCCN Guidelines Gastric Cancer, 2019). Despite these treatment options, the overall clinical outcomes for patients with advanced/metastatic GEC remain poor, and novel treatment strategies are needed.

A recent review suggests that anti-PD-1 agents will be standard of care as front-line treatment of GEC (Smyth et al, 2021). On 16 April 2021, the US Food and Drug Administration approved

nivolumab to be combined with select types of chemotherapy for initial treatment of patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma (US Food and Drug Administration 2021). First-line treatment with the combination of nivolumab and chemotherapy demonstrated a statistically significant improvement in OS among previously untreated patients with PD-L1-positive advanced gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma compared to chemotherapy alone (CHECKMATE-649; NCT02872116). CHECKMATE-649 demonstrated a statistically significant improvement in OS and PFS for patients with PD-L1 combined positive score (CPS) ≥5. Median OS was 14.4 months (95% confidence interval [CI]: 13.1, 16.2) in the nivolumab plus chemotherapy arm versus 11.1 months (95% CI: 10.0, 12.1) in the chemotherapy alone arm (hazard ratio [HR] 0.71; 95% CI: 0.61, 0.83; p<0.0001). Median PFS was 7.7 months (95% CI: 7.0, 9.2) in the nivolumab plus chemotherapy arm versus 6.0 months (95% CI: 5.6, 6.9) in the chemotherapy alone arm (HR 0.68; 95% CI: 0.58, 0.79; p<0.0001). A statistically significant improvement in OS was also demonstrated for all randomized patients irrespective of CPS. Furthermore, nivolumab plus chemotherapy also resulted in a 32% reduction in the risk of disease progression or death compared with chemotherapy alone (HR, 0.68; 95% CI, 0.56-0.81; p<0.0001) (Moehler et al, 2018, Moehler et al, 2021, OPDIVO PI 2021). In light of this recent approval of a new first-line treatment standard of care for these patients, Trishula is amending this protocol. In consideration of the new approved standard of care, Trishula feels it is no longer appropriate to randomize subjects to a treatment arm that does not include a checkpoint inhibitor in addition to chemotherapy. Effective 1 June 2021, all new subjects who enroll in Cohort 3 will be assigned to the remaining treatment Arm B (TTX-030 + anti-PD-1 [ABBV-181] + mFOFLOX6). In addition, a treatment arm using budigalimab, a checkpoint inhibitor, would be expected to have activity in GEC when combined with chemotherapy.

2.2.1.2 Colorectal Cancer

Worldwide, approximately 1.8 million new cases of colorectal cancer (CRC) and more than 850,000 associated deaths were reported in 2018 (Bray et al, 2018). In the US, it is estimated that more than 150,000 new cases of CRC will be diagnosed in 2019, and there will be approximately 50,000 CRC-related deaths (Siegel et al, 2020). Approximately 50% to 60% of patients diagnosed with CRC will develop metastatic disease, and the liver is the most common site of involvement (NCCN Guidelines Colon Cancer, 2019). About 80% to 90% of patients who develop metastatic CRC will have unresectable liver metastases, and many will require systemic therapy. For most of those patients, treatment is palliative and not curative.

For decades, 5-fluorouracil (5-FU) was the sole active agent for the systemic treatment of advanced metastatic CRC. However, that changed dramatically beginning in 2000 with the approval of several 5-FU-based regimens containing oxaliplatin and/or irinotecan (FOLFOX, FOLFIRI, and FOLFIRINOX) and the addition of antiangiogenic agents and inhibitors of the epidermal growth factor receptor (EGFR) to standard chemotherapy (Clark and Grothey, 2018). Several agents that inhibit angiogenesis by targeting vascular endothelial growth factor or its receptors have been approved for metastatic CRC. These include bevacizumab, ramucirumab, aflibercept, and regorafenib. Agents that target EGFR include cetuximab and panitumumab. Consequently, a wide range of combination regimens are approved as first-line therapy for metastatic CRC (NCCN Guidelines Colon Cancer, 2019). The choice and intensity of therapy depend on treatment goals, type and timing of prior therapies, the mutational profile of the tumor,

and toxicities of the agents. Guidelines do not provide a preference for any regimen over another (NCCN Guidelines Colon Cancer, 2019). Most patients deemed appropriate for intensive therapy will receive an infusional 5-FU-based combination chemotherapy regimen plus either bevacizumab or an EGFR inhibitor as first-line therapy. However, only patients shown to be wild-type for KRAS and NRAS should be treated with an EGFR inhibitor (NCCN Guidelines Colon Cancer, 2019). For patients not eligible for intensive therapy, 5-FU or capecitabine, with or without bevacizumab, anti-EGFR monotherapy, and immunotherapy are recommended (NCCN Guidelines Colon Cancer, 2019). The PD-1 inhibitors nivolumab and pembrolizumab can be used when the tumor is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), which are associated with a high mutational burden, rendering the tumor more responsive to immunotherapy (NCCN Guidelines Colon Cancer, 2019).

All of the regimens recommended as first-line therapy can be used in the second- and third-line settings in a continuum of care. Choice of second-line therapy is largely dependent on prior therapy, response to prior therapy, and how well the patient tolerated it. Although few studies have addressed the optimum sequencing of therapies for advanced metastatic CRC, studies have shown that outcomes are similar whether intensive therapy is given first or second-line (NCCN Guidelines Colon Cancer, 2019). The antiangiogenic agents bevacizumab, ramucirumab, aflibercept, and regorafenib are approved for use as second-line therapy for metastatic CRC; regorafenib is recommended as third-line therapy. There is also considerable interest in the use of maintenance therapy with a less intensive regimen (e.g., capecitabine, oxaliplatin, and bevacizumab) after a patient has achieved stable disease (SD) or better with an intensive first-line regimen. This approach has been shown to significantly improve second PFS in the CAIRO3 and AIO 0207 trials (Simkens et al, 2015; Hegewisch-Becker et al, 2015). However, the PRODIGE 9 and SAKK 41/06 trials reported no evidence that maintenance therapy with bevacizumab monotherapy improves tumor control of time to progression (Aparicio et al, 2018; Koeberle et al, 2015).

2.2.1.3 Head and Neck Squamous Cell Carcinoma

Head and neck cancer is a heterogeneous group of squamous cell cancers that affects the oral cavity, pharynx, and larynx. The incidence of head and neck squamous cell carcinoma (HNSCC) varies greatly depending on the anatomic site and geographic region. Worldwide, approximately 835,000 new cases and approximately 431,000 deaths related to HNSCC were estimated in 2018 (Bray et al, 2018). In the US, approximately 65,000 new cases and 14,000 deaths related to HNSCC were estimated in 2019 (Siegel et al, 2020). Historically, the etiology of HNSCC was associated with smoking and alcohol, but human papillomavirus (HPV), which is currently the most common sexually transmitted disease in the US (Berman and Schiller, 2017), has increasingly been recognized as another primary cause of HNSCCs. In fact, a significant subset of oropharyngeal cancers (OPCs) is driven by HPV infection. Over the past 20 years, the frequency of HPV detection in OPC has increased from 16% to 73% in the US. Today, an estimated 70% to 80% of OPCs in the US and Europe are attributed to HPV infection, which is due to the high prevalence of oral HPV type 16 infections in these regions. Other high-risk HPV genotypes, such as HPV-18, -31, or -33, are also causative but are less common. HPV-positive OPCs have different clinicopathologic features compared with HPV-negative HNSCC that affect staging, prognosis, and treatment (Haddad, 2018). HPV-positive tumors primarily occur in the tonsillar region or base of the tongue, mainly in men, and these patients are generally younger

and healthier and have a better prognosis than patients with HPV-negative HNSCC. Therefore, diagnostic guidelines recommend evaluating all OPCs for HPV infection (NCCN Guidelines Head and Neck Cancers, 2019). Although some non-OPCs are HPV-related, there is currently insufficient evidence to recommend HPV testing in these patients (NCCN Guidelines Head and Neck Cancers, 2019). In HPV-positive OPC, immunohistochemistry (IHC) of the tumor suppressor protein, known as p16, is currently used as a surrogate HPV biomarker (Evans et al, 2013). Current diagnostic algorithms advocate screening of p16 IHC followed by detection of HPV DNA using either polymerase chain reaction (PCR) or in situ hybridization (Evans et al, 2013).

The conventional approach for managing advanced-stage HNSCC, regardless of HPV status, involves multimodal therapy with concurrent cisplatin-based chemotherapy plus radiotherapy or surgery, followed by adjuvant radiotherapy with or without chemotherapy (Berman and Schiller, 2017; NCCN Guidelines Head and Neck Cancers, 2019). This traditional treatment paradigm is associated with significant toxicity. HPV-positive tumors respond well to chemotherapy and radiotherapy, possibly because they typically have a wild-type p53 tumor suppressor gene, which is silenced by the virus, rather than a mutated p53 gene (Berman and Schiller, 2017). Consequently, studies are ongoing to investigate de-escalated treatment regimens for HPV-positive OPC (Berman and Schiller, 2017; Haddad, 2018; Vokes et al, 2015). This should result in less toxicity and morbidity in this patient population. The addition of cetuximab to chemotherapy or radiotherapy has been shown to improve locoregional control and OS (Berman and Schiller, 2017). For example, the EXTREME regimen, which combines cetuximab with standard platinum-fluorouracil chemotherapy followed by maintenance cetuximab, is commonly used in first-line-treatment of recurrent/metastatic disease and shows the best median OS (10 months) (NCCN Guidelines Head and Neck Cancers, 2019; Vermorken et al, 2008). Beyond first line; however, few drugs can be used (e.g., taxanes and methotrexate), and the median OS drops to 6 months, indicating the need for novel therapies to improve the prognosis of HNSCC in this setting (Echarri et al, 2016).

Emerging data have demonstrated that immune checkpoint inhibitors are efficacious and well-tolerated in advanced HNSCC. The PD-1 inhibitors pembrolizumab and nivolumab were approved in 2016 for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after a platinum-based therapy. In the Phase 3 study that supported the approval of pembrolizumab in this population, treatment with pembrolizumab (200 mg every 3 weeks) resulted in a significantly longer median OS than standard of care (i.e., Investigator's choice of standard doses of methotrexate, docetaxel, or cetuximab) (8.4 vs 6.9 months; p=0.0161; Cohen et al, 2019). Fewer patients treated with pembrolizumab than standard of care had Grade ≥3 treatment-related adverse events (AEs) (13% vs 36%). In the Phase 3 study that supported the approval of nivolumab in recurrent HNSCC who progressed on platinum-based chemotherapy, median OS was 7.5 months with nivolumab (3 mg/kg every 2 weeks [Q2W]) versus 5.1 months in the standard therapy group (i.e., methotrexate, docetaxel, or cetuximab) (p=0.01), and the 1-year survival rate was 19 percentage points higher with nivolumab than standard therapy (36.0% vs 16.6%; Ferris et al, 2016). Response rate was 13.3% in the nivolumab group versus 5.8% in the standard therapy group. Treatment-related events of Grade 3 or 4 occurred in 13.1% of nivolumab-treated patients and in 35.1% of patients in the standard therapy group.

2.2.1.4 Metastatic Castration-resistant Prostate Cancer

Prostate cancer is the second most frequently diagnosed malignancy and the fifth leading cause of cancer-related death in men worldwide (Bray et al, 2018). In 2018, more than 1.2 million new prostate cancer cases and 359,000 associated deaths were estimated to occur. In the US, an estimated 175,000 new cases of prostate cancer will be diagnosed in 2019, and there will be approximately 32,000 prostate cancer-related deaths (Siegel et al, 2020). Prostate cancer deaths are typically the result of metastatic castration-resistant prostate cancer (mCRPC), and historically, the median survival for men with mCRPC has been <2 years (Cookson et al, 2013).

Recent research has expanded the therapeutic options for patients with mCRPC depending on the presence or absence of symptoms (NCCN Guidelines Prostate Cancer, 2019). For patients with minimal symptoms, secondary hormonal therapy is the first-line option and can include a second-generation antiandrogen (enzalutamide), androgen metabolism inhibitor (abiraterone and prednisone/methylprednisolone), or other secondary hormone therapy (ketoconazole with or without hydrocortisone, first-generation antiandrogen, corticosteroids, diethylstilbestrol or other estrogens, and antiandrogen withdrawal). Studies evaluating the addition of abiraterone or enzalutamide prior to docetaxel chemotherapy reported median OS in the range of 4.4 to 4.8 months (Fizazi et al, 2012; Ryan et al, 2015; Scher et al, 2012). For patients with symptomatic mCRPC, chemotherapy with docetaxel and concurrent steroid is the preferred first-line treatment option, although all of the secondary hormone options listed above are allowed (NCCN Guidelines Prostate Cancer, 2019). Radium-223 has been studied in symptomatic patients who are not candidates for docetaxel-based regimens and resulted in improved OS over placebo (14.0 vs 11.2 months; Parker et al, 2013). In addition, patients who are not candidates for docetaxel or who are intolerant of docetaxel should be considered for cabazitaxel with concurrent steroid, based on recent results that suggested clinical activity in mCRPC and less toxicity (i.e., lower rates of peripheral neuropathy) than docetaxel. Cabazitaxel with concurrent steroid has been shown in a randomized Phase 3 study (TROPIC) to prolong OS and PFS compared with mitoxantrone and prednisone in patients who progressed during or after docetaxel chemotherapy (de Bono et al, 2010). Cabazitaxel is approved by the US Food and Drug Administration for mCRPC in the post-docetaxel second-line setting.

Immunotherapy may be considered in men with asymptomatic or minimally symptomatic mCRPC. Sipuleucel-T is only indicated for asymptomatic or minimally symptomatic mCRPC without liver metastases. In a Phase 3 trial (IMPACT), sipuleucel-T has been shown to improve OS by 4.1 months in asymptomatic or minimally symptomatic chemotherapy-naïve mCRPC patients (Kantoff et al, 2010). Pembrolizumab, which is indicated for tumors that are MSI-H or dMMR, is only recommended as subsequent systemic therapy for patients who have progressed through at least 1 line of systemic therapy for mCRPC. In studies of pembrolizumab monotherapy, with identical durations of follow-up, median OS was 7.9 months in PD-L1-negative disease, 9.5 months in PD-L1-positive disease, and 14.1 months in nonmeasurable bone-predominant disease (Antonarakis et al, 2019).

In a combination study of nivolumab and docetaxel in mCRPC subjects (n=41) who were eligible for docetaxel, preliminary result reported a confirmed objective response rate (ORR) of 36.8% (n=19 with measurable disease) and a confirmed prostate-specific antigen (PSA) response rate of 46.3% (n=41). The median radiologic PFS of 8.2 months indicates potentially greater clinical

activity relative to docetaxel alone based on other available historical data in a similar population. The overall safety profile demonstrated an acceptable safety profile (Fizazi et al, 2019).

Overall, despite the therapeutic advances in mCRPC, there continues to be an unmet medical need in the later-line settings.

2.2.1.5 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 US, approximately 57,000 new cases and 47,000 deaths related to pancreatic cancer were estimated in 2019 (Siegel et al, 2020).

One of the preferred first-line systemic treatment for locally advanced pancreatic adenocarcinoma is gemcitabine and nab-paclitaxel (NCCN Guidelines Pancreatic Adenocarcinoma, 2021).

2.2.1.6 Urothelial Cell Carcinoma

Urothelial cancer occurs in urothelial cells that line the urethra, bladder, ureters, renal pelvis, and some other organs. Worldwide, approximately 549,393 new cases and 199,922 deaths related to bladder cancer were estimated in 2018 (Bray et al, 2018). In the US, approximately 81,000 new cases and 18,000 deaths related to urothelial cancer were estimated in 2019 (Siegel et al, 2020).

Systemic therapy for bladder cancer depends on platinum eligibility; one of the preferred regimens is pembrolizumab for patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression (NCCN Guidelines Bladder Cancer, 2020).

2.2.2 Background on TTX-030

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

2.2.2.1 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. This antibody does bind to and inhibit cynomolgus monkey CD39 but is not cross-reactive with murine CD39. 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 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.

Multiple-dose 28-day Good Laboratory Practice (GLP) toxicology studies in cynomolgus monkey did not show any TTX-030-related findings, and doses up to 100 mg/kg were well tolerated. These animals were dosed IV with 0, 30, or 100 mg/kg of TTX-030 once per week for 4 weeks (5 total doses). TTX-030 was non-immunogenic at all dose levels as serum antidrug antibody (ADA) levels in all TTX-030-treated monkeys remained below or near pretreatment levels. The no-observed-adverse-effect level for the repeat-dose study was 100 mg/kg.

2.2.2.2 Summary of Clinical Experience With TTX-030

TTX-030 is being evaluated in 2 ongoing clinical studies and preliminary safety data are described below:

- Study TTX-030-001, a first-in-human Phase 1/1b study of TTX-030 as monotherapy or in combination with pembrolizumab or chemotherapy in subjects with lymphoma or solid tumors.

- Study TTX-030-002, a Phase 1/1b study of TTX-030 combination therapy in subjects with advanced solid tumors.

2.2.2.2.1 Study TTX-030-001

Study TTX-030-001 was conducted in 2 parts: TTX-030 was evaluated in monotherapy dose escalation to determine the recommended Phase 2 dose (RP2D; Part A) and TTX-030 was evaluated as monotherapy or combination therapy (anti-PD-1 [pembrolizumab] in solid tumors or chemotherapy [gemcitabine and nab-paclitaxel] in pancreatic cancer) at the RP2D (Part B). During Part A of the study, the RP2D was determined to be 40 mg/kg loading dose 7 days prior to Cycle 1 Day 1, followed by either 30 mg/kg Q3W (in combination with pembrolizumab) or 20 mg/kg Q2W (in combination with gemcitabine and nab-paclitaxel).

As of the data cutoff date of 30 December 2020, 21 subjects in Study TTX-030-001 have received TTX-030 monotherapy Q3W at the following escalating doses: 0.5 mg/kg (n=1), 1.5 mg/kg (n=2), 3.0 mg/kg (n=2), 6.0 mg/kg (n=4), 10 mg/kg (n=3), 20 mg/kg (n=3), or 40 mg/kg (n=6) in Part A of the study. A total of 19 subjects have received TTX-030 as monotherapy or in combination in the following dose-expansion cohorts: TTX-030 40 mg/kg load; 30 mg/kg Q3W and pembrolizumab (n=11), TTX-030 40 mg/kg load; 30 mg/kg Q3W monotherapy (n=4), and TTX-030 40 mg/kg load; 20 mg/kg Q2W, gemcitabine, and nab-paclitaxel (n=4) in Part B of the study.

Doses of TTX-030 monotherapy up to 40 mg/kg Q3W in the dose-escalation phase have been well tolerated and no dose-limiting toxicities (DLTs) were observed. Most treatment-emergent adverse events (TEAEs) were Grade 1 or 2 in severity. Although TEAE resulting in death (4.8%), TEAEs leading to study drug withdrawal (14.3%), serious TEAEs (38.1%), and Grade 3 or 4 TEAEs (42.9%) occurred, none were considered related to TTX-030.

In the dose Expansion Phase, doses of TTX-030 as combination therapy (40 mg/kg load, followed by 20 mg/kg Q2W or 30 mg/kg Q3W) have been well tolerated. Most TEAEs were

Grade 1 or 2 in severity. TTX-030-related serious TEAEs (15.8%) included autoimmune hepatitis, colitis, and generalized oedema (1 subject each). TTX-030-related Grade 3 or higher TEAEs (21.1%) included amylase increased, autoimmune hepatitis, fatigue, generalized oedema, and lipase increased (1 subject each). No TTX-030-related TEAEs led to TTX-030 withdrawal or resulted in death.

PK parameters for Study TTX-030-001 were estimated for doses from 6 to 40 mg/kg. The elimination half-life ($t_{½\beta}$) and clearance (CL) over that dose range averaged 18.9 days and 0.385 mL/h/kg, respectively. In Study TTX-030-001, the RP2D was determined to be 40 mg/kg loading dose 7 days prior to Cycle 1 Day 1, followed by either 30 mg/kg Q3W (in combination with pembrolizumab) or 20 mg/kg Q2W (in combination with gemcitabine and nab-paclitaxel) to provide a minimal functional trough level.

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

2.2.2.2.2 Study TTX-030-002

As of the data cutoff date of 30 December 2020, 12 subjects have received TTX-030 in combination in the safety lead-in phase (8 subjects with solid tumors and 4 subjects with mCRPC). A total 27 subjects have received TTX-030 in combination (1 subject with HER2 GEC [Arm A Cohort 3], 1 subject with HER2 GEC [Arm B Cohort 3], 14 subjects with CRC [Cohort 4], 4 subjects with recurrent/metastatic HNSCC [Cohort 6], 7 subjects with advanced HER2 GEC [Cohort 8]).

In the safety lead-in, doses of TTX-030 as combination therapy (40 mg/kg load, followed by 20 mg/kg Q2W or 30 mg/kg Q3W) were well tolerated. TTX-030-related Grade 3 or 4 TEAE (16.7%) included neutrophil count decreased, pneumonitis, and rash maculo-papular (1 subject each). TTX-030-related serious TEAEs (8.3%) included rash maculo-papular (1 subject). Treatment-related TEAEs leading to TTX-030 study drug withdrawal (8.3%) included intestinal obstruction (1 subject). No TTX-related TEAEs resulted in death.

In the dose Expansion Phase, doses of TTX-030 as combination therapy (40 mg/kg load, followed by either 30 mg/kg Q3W or 20 mg/kg Q2W) have been well tolerated. Most TEAEs were Grade 1 or 2 in severity. TTX-030-related serious TEAEs (3.7%) included acute kidney injury (1 subject). TTX-030-related Grade 3 or higher TEAEs (3.7%) included acute kidney injury (1 subject). No TTX-030-related TEAEs led to TTX-030 withdrawal or resulted in death.

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

2.2.3 Background on Budigalimab (ABBV-181)

Budigalimab is a [redacted] 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 PD-L1 and programmed cell death ligand-2 with high potency in multiple assay formats. The affinity of budigalimab [redacted] 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.

2.2.3.1 Summary of Nonclinical Experience with Budigalimab

The toxicity profile of budigalimab was evaluated in cynomolgus monkeys due to cross-reactivity of budigalimab to cynomolgus PD-1. In vivo toxicity studies included a 3-week non-GLP dose-range-finding study (intravenous [IV] bolus once weekly for 4 doses), a 4-week GLP toxicity study (IV bolus once weekly for 5 doses, followed by a 16-week recovery period), a 13-week toxicity study (IV bolus once every other week for 7 doses), and a 2-week GLP toxicity study (subcutaneous route of administration on Day 1 and Day 15 for 2 doses). An in vitro hemolysis and plasma compatibility assay, a human tissue cross-reactivity study, and an in vitro immunosafety assessment were also conducted with budigalimab.

Administration of budigalimab at doses of up to 100 mg/kg/dose was well tolerated in the dose-range-finding study. Findings included mild to moderate, non-dose-dependent decreases in lymphocytes 24 hours following the first dose at ≥10 mg/kg/dose and minimal sciatic nerve fiber degeneration at 30 mg/kg/dose.

Toxicity in the 4-week GLP study was limited to effects on red blood cell mass and sciatic nerve fiber at ≥30 mg/kg/dose. Hematologic changes (decreased red blood cell mass, increased reticulocytes, and morphologic changes) were observed at 30 and 100 mg/kg/dose. The most pronounced effects occurred in a female animal at 100 mg/kg/dose following 2 doses; further dosing in this animal was discontinued. Similar but less severe, reversible effects were observed among several animals at ≥30 mg/kg/dose. The possibility of hemolysis due to budigalimab-related increased activation of the immune system could not be excluded, particularly based on the pronounced effects in the one high-dose female. Adverse nerve fiber degeneration (sciatic nerve) was observed microscopically among animals at ≥30 mg/kg/dose and considered related to budigalimab administration.

Based upon the adverse histopathology findings observed at ≥30 mg/kg/week, the no-observed-adverse-effect level (NOAEL) was deemed to be 10 mg/kg. The highest non-severely toxic dose (HNSTD) was determined to be 30 mg/kg based on the intolerability of budigalimab in 1 animal at 100 mg/kg.

In the 13-week toxicity study, changes associated with budigalimab administration were limited to non-dose-dependent increases in the incidence of soft/watery feces in males. No other budigalimab-related changes were observed via clinical observations, body weight, electrocardiogram (ECG), ophthalmoscopic evaluations, or clinical and anatomic pathology. One unscheduled euthanasia that was not considered budigalimab related occurred in Week 12 for 1 female at the 10 mg/kg dose; this animal exhibited persistent watery feces and declining physical condition. A definitive cause for persistent watery feces could not be determined; however, abundant *Balantidium coli* was observed on fecal smear. The NOAEL and the HNSTD in this study were determined to be 100 mg/kg (highest dose tested). A final report for this study is pending.

The proposed starting dose in the first-in-human study was 1 mg/kg. The 10 mg/kg (NOAEL) and the 30 mg/kg (HNSTD) in cynomolgus monkeys provide approximately 8-fold and 27-fold exposure margin (area under the concentration curve), respectively, when compared with the predicted human exposures at the 1 mg/kg starting dose.

Administration of budigalimab via the subcutaneous route of administration was well tolerated in nonclinical animal models up to the highest dose evaluated, 50 mg/kg. This study was conducted to support subcutaneous (SC) administration for the human immunodeficiency virus (HIV) indication.

The cumulative toxicology and pharmacokinetic (PK) data from preclinical studies indicate that the nonclinical safety profile of budigalimab has been adequately characterized to support the initiation of investigational trials with this compound in humans. The early clinical development plan for budigalimab is based on the clinical activity demonstrated for PD-1 antagonistic antibodies in patients with solid tumors and HIV.

2.2.3.2 Summary of Clinical Experience with Budigalimab

To date, 12 Phase 1 clinical studies of budigalimab (ABBV-181) have been initiated, 9 studies are ongoing. Clinical data are available for subjects in 8 studies. Preliminary safety data are available for 142 subjects treated with budigalimab as monotherapy in Study M15-891 (N=140) and Study M19-228 (N=2); preliminary safety data are also available for 212 subjects treated in the budigalimab combination with other agents.

Summary of Safety

As of October 2020, the budigalimab clinical program comprises 12 Phase 1 studies evaluating budigalimab administration as monotherapy in 142 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 212 subjects. Preliminary data are available for Studies M15-891, M19-228, M14-006, M15-862, M16-074, SCRX003-001, M16-312, and M19-345.

Preliminary safety data were available for 142 subjects administered budigalimab as monotherapy in Study M15-891 and Study M19-228. Adverse events were reported for 140 subjects (98.6%).

Preliminary safety data are also available for 212 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=52)
- 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=31)

Oncology - Budigalimab Monotherapy

As of October 2020, preliminary clinical safety data were available for 140 subjects who received budigalimab monotherapy in Study M15-891. Overall, treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) were reported for 98.6% and 54.3% of subjects, respectively. The most commonly reported AEs (occurring in >10% of subjects) were anemia, hypothyroidism, constipation, diarrhea, nausea, vomiting, asthenia, fatigue, pyrexia, decreased

appetite, malignant neoplasm progression, tumor pain, headache, cough, dyspnea, and pruritus. The most commonly reported SAEs (occurring in ≥3 subjects) were malignant neoplasm progression, pneumonia, pyrexia, acute kidney injury, upper respiratory tract infection, tumor hemorrhage, and dyspnea.

Adverse events that were considered immune-mediated by the investigator were reported for 33.6% of subjects; the most commonly reported immune-mediated AEs (occurring in >5% of subjects) were hypothyroidism, diarrhea, and pruritus. Grade ≥3 TEAEs were reported in 65.7% of subjects; 9.3% of subjects had Grade ≥3 TEAEs that were considered possibly related to budigalimab. TEAEs leading to budigalimab discontinuation were reported in 27.1% of subjects; malignant neoplasm progression (11 subjects) and pneumonitis (2 subjects) were the only events that resulted in discontinuation for >1 subject. Thirty-one subjects who received budigalimab monotherapy had TEAEs leading to death; no deaths were assessed as possibly related to budigalimab and the only event leading to death that occurred in >1 subject was malignant neoplasm progression.

In addition, preliminary safety data are available for 2 subjects treated with budigalimab as monotherapy in Study M19-228. Two subjects (100%) who received budigalimab as monotherapy reported AEs; all AEs occurred in 1 subject each.

Oncology - Budigalimab in Combination Therapy

As of October 2020, preliminary clinical safety data were available for 212 subjects who received budigalimab as combination therapy. Overall, TEAEs were reported for all subjects (100.0%) across studies, except Study M16-074 where 52 subjects (94.5%) reported AEs and Study M19-345 where 30 subjects (96.8%) reported AEs. The most frequently reported AEs (occurring in ≥10 subjects in any given study) across budigalimab combination therapy studies were nausea, asthenia, fatigue, pyrexia, decreased appetite, pleural effusion, and pruritus. Reported SAEs across combination therapy studies ranged from 28.6% to 66.7% of subjects; the most commonly reported SAEs (occurring in ≥3 subjects in any given study) were thrombocytopenia, pyrexia, pneumonia, malignant neoplasm progression, pleural effusion, and dyspnea.

Reported AEs considered immune-mediated across combination therapy studies ranged from 10.9% to 45.2%; immune-mediated AEs reported in ≥2 subjects in any given study included colitis, decreased appetite, lymphopenia, pneumonitis, pruritus, rash, and rash maculo-papular.

Reported Grade ≥3 TEAEs in any given study ranged from 28.6% to 85.7%; Grade 3 or higher events with a reasonable possibility of being related to budigalimab and occurring in ≥2 subjects in any given study were lymphopenia, fatigue, alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, and hypertension. Reported TEAEs leading to discontinuation of treatment with budigalimab ranged from 9.6% to 42.9% of subjects; TEAEs leading to discontinuation in >1 subject included disease progression and malignant neoplasm progression (Study M16-074); all other events occurred in 1 subject each. Reported AEs leading to death across combination therapy studies ranged from 0 to 22.2% of subjects. No subjects reported events leading to death in Study SCRX003-001. Events leading to death across combination therapies with budigalimab in ≥2 subjects in any given study was malignant neoplasm progression (3 subjects each in Studies M15-891 [budigalimab + Rova-T], M15-862, M16-074, and M19-345; and 2 subjects in Study M16-312). One event of respiratory failure (Study M16-074) leading to death was considered to have a reasonable possibility of being related to budigalimab.

Based on the available clinical data (as of October 2020), the safety profile of budigalimab is consistent with those identified with other agents targeting the PD-1 receptor, and no unique toxicities have been observed.

Oncology - Summary of Efficacy

As of October 2020, preliminary efficacy data are available for 140 subjects treated with budigalimab monotherapy in Study M15-891. [redacted]

As of October 2020, preliminary efficacy data are available for 31 subjects treated with budigalimab + Rova-T in Study M15-891. [redacted]

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

2.2.4 Background on mFOLFOX6

mFOLFOX6 is a combination chemotherapy regimen that includes the drugs leucovorin (folinic acid), 5-FU, and oxaliplatin. Refer to the prescribing information of oxaliplatin for details (ELOXATIN PI, 2015).

2.2.5 Rationale for Combining TTX-030 with Budigalimab and/or mFOLFOX6

In this study, subjects will be treated with combinations of up to 3 different drugs, including 2 experimental immunotherapies, one that inhibits the enzyme (CD39) responsible for the phosphohydrolysis of extracellular ATP (TTX-030) and one that inhibits the PD-1 checkpoint (budigalimab), and chemotherapy (mFOLFOX6).

While impressive and durable responses are observed in subsets of patients treated with anti-PD-1 agents, response rates are rarely >50%, and, for most patients, a response is transient. Thus, a synergistic strategy may be beneficial for patients. 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 make the tumor more susceptible to 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 the control or either monotherapy. Anti-PD-1 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).

Chemotherapy remains a key therapeutic option for many cancer patients, and it has been conventionally believed to directly kill tumor cells through their cytotoxic effects and trigger tumor cell death in a nonimmunogenic manner. However, accumulating evidence indicates that some traditional chemotherapeutic agents (including anthracyclines and oxaliplatin) 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. Blockade of CD39-mediated ATP hydrolysis with TTX-030 would therefore enhance accumulation of proinflammatory ATP in the tumor microenvironment. Enhancing ATP concentrations to levels that bind and activate purinergic receptors, such as P2X7, would 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 synergy when combining CD39 inhibitors with chemotherapy.

Together, these findings suggest that TTX-030 combined with budigalimab and/or mFOLFOX6 has the potential to induce tumor control in cancer patients and be viable combinations in the clinic.

2.2.6 Rationale for Combining Budigalimab and mFOLFOX6

Please refer to Section 2.2.1.1.

2.2.7 Background on Docetaxel

Treatment with docetaxel 75 mg/m^2 Q3W is widely used in lung, breast, prostate, bladder, and other cancers (TAXOTERE PI, 2019).

2.2.8 Rationale for Combining TTX-030 with Budigalimab and Docetaxel

TTX-030 is postulated to potentiate the effectiveness of TTX-030 with budigalimab and docetaxel combination-therapy regimen.

PD-1 and docetaxel agents have been approved and/or used as standard of care as single agent in several indications and have a well-characterized safety profile as described in Section 2.2.1.4. The recent study of nivolumab and docetaxel combination also demonstrated positive clinical antitumor activity and an expected safety profile in PD-1 and docetaxel combination (Fizazi et al, 2019). TTX-030 has a different mechanism of action in the combination arms, and toxicities are anticipated to be manageable and nonoverlapping.

2.2.9 Background on Gemcitabine + nab-Paclitaxel

Treatment with gemcitabine 1000 mg/m^2 nab-paclitaxel 125 mg/m^2 is widely used in the treatment of metastatic pancreatic cancer (GEMZAR PI 2019 and ABRAXANE PI, 2020).

2.2.10 Rationale for Combining TTX-030 with Budigalimab and Gemcitabine/nab-Paclitaxel

Adding budigalimab to establish a triplet regimen (gemcitabine/nab-paclitaxel + TTX-030 + budigalimab) may increase the efficacy of gemcitabine/nab-paclitaxel, while toxicities may remain manageable.

Cohort 1 (safety lead-in of TTX-030 + budigalimab + mFOLFOX6 combination) also represents the safety lead-in for triplet combination of gemcitabine/nab-paclitaxel + TTX-030 + budigalimab administered in Cohort 9 (see also Section 4.1.1.1).

2.2.11 Rationale for Combining TTX-030 and Gemcitabine plus nab-Paclitaxel

TTX-030 may increase the effectiveness of gemcitabine/nab-paclitaxel. TTX-030 has a different mechanism of action from this regimen, and toxicities are anticipated to be manageable and nonoverlapping.

2.2.12 Background on Pembrolizumab

Treatment with pembrolizumab 200 mg Q3W is widely used in melanoma, non-small cell lung cancer, small cell lung cancer, Hodgkin lymphoma, primary mediastinal large B-cell lymphoma, urothelial carcinoma, colorectal cancer, gastric cancer, esophageal cancer, cervical cancer, hepatocellular carcinoma, Merkel cell carcinoma, renal cell carcinoma, endometrial carcinoma, cutaneous squamous cell carcinoma, triple-negative breast cancer as monotherapy or in combination therapy (KEYTRUDA PI, 2020).

2.2.13 Rationale for Combining TTX-030 with Pembrolizumab

Pembrolizumab has been approved and used as standard of care in several indications. The rationale for combining TTX-030 with pembrolizumab, an anti-PD1 agent, is described in Section 2.2.5.

2.3 Benefit-Risk Assessment

This section summarizes the benefit-risk profile for each of the drugs (TTX-030, budigalimab, mFOLFOX6, docetaxel, gemcitabine + nab-paclitaxel, and pembrolizumab) 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 TTX-030 in combination with pembrolizumab or budigalimab and/or chemotherapy are judged acceptable for this clinical study.

2.3.1 TTX-030 Risks and Benefits

Blockade of CD39 may result in less potential for autoimmune side effects compared with rates seen with other immunotherapy agents. Although regulatory T cells from CD39KO mice have impaired suppressive activity, the mice do not show autoimmunity (Sun et al, 2010).

TTX-030 has a different mechanism of action from each of the regimens to be used in combination arms, and toxicities are anticipated to be manageable and nonoverlapping. It is conceivable that the dose of TTX-030 given in combination with budigalimab and/or

mFOLFOX6 may be the same or near the dose for TTX-030 given as a single agent. Conversely, it is also possible that TTX-030 could potentiate some of the existing toxicities of the combination regimens.

The clinical risks and benefits of TTX-030 are unknown at this time; however, several investigational agents targeting adenosine receptors and CD73 in the adenosine pathway have reportedly entered Phase 1 trials and may offer insights on potential risks and benefits of targeting the adenosine pathway. 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). A similar safety profile was observed with NIR178 (previously known as PBF-509), also a small-molecule inhibitor of the $A_{2a}R$, which has been evaluated both in healthy volunteers (NCT01691924 and NCT02111330) and in patients with advanced NSCLC (NCT02403193). NIR178 was reportedly well-tolerated. AEs were manageable and there were no Grade 4 drug-related AEs; immune-related AEs (irAEs) may indicate immune stimulation (Chiappori et al, 2018). 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), GEC or CRC (NCT03720678), and solid tumors (NCT03629756). Preliminary data showed a favorable safety profile, with no Grade 4 or 5 AB928-related AEs reported to date across the studies (Powderly et al, 2019).

Antibodies targeting CD73 have also recently entered clinical development. Data from NZV930/SFF3737 (NCT03549000) and CPI-006 (NCT03454451) have not been reported. 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 other investigational agents targeting $A_{2a}R$ and CD73 in the adenosine pathway were shown to be well tolerated. Publicly disclosed safety data have been summarized in more detail in the Investigator's Brochure.

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 patients with metastatic NSCLC, melanoma, and renal cell carcinoma; Anagnostou et al, 2015). 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 mFOLFOX6 Risks and Benefits

The benefit-risk profile of mFOLFOX6 is well established. Its efficacy and safety in the treatment of GEC and CRC have been described in Section 2.2.1.1 and Section 2.2.1.2, respectively.

2.3.4 Docetaxel Risks and Benefits

The benefit-risk profile of docetaxel is well established. Its efficacy and safety in the treatment of mCRPC have been described in Sections 2.2.1.4, 2.2.7, and 2.2.8, respectively.

2.3.5 Gemcitabine and nab-Paclitaxel Risks and Benefits

The benefit-risk profile of gemcitabine and nab-paclitaxel is well established. Its efficacy and safety in the treatment of pancreatic adenocarcinoma have been described in Section 2.2.1.5.

Refer to product label for risks and benefits (GEMZAR PI 2019 and ABRAXANE PI, 2020).

2.3.6 Pembrolizumab Risks and Benefits

The benefit-risk profile of pembrolizumab is well established. Its efficacy and safety in the treatment of UCC have been described in Section 2.2.1.6.

Refer to product label for risks and benefits (KEYTRUDA PI, 2020).

3 OBJECTIVES AND ENDPOINTS

The study objectives and corresponding endpoints are presented in Table 5.

Table 5: Objectives and Endpoints

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

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

4 STUDY DESIGN

4.1 Description of the Study

4.1.1 Overview

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

The study schema is depicted in Figure 1.

4.1.1.1 Safety Lead-in

The Safety Lead-in Phase includes 2 cohorts as described below and will identify the doses of TTX-030 and budigalimab in combination with chemotherapy or other therapy to be evaluated in the Expansion Phase. The Cohort Review Committee (see Section 4.1.2) will monitor each cohort during the DLT evaluation period (28-day for TTX-030 regimens given every 2 weeks [Q2W] or 21-day for TTX-030 regimens given every 3 weeks [Q3W] plus a loading dose 7 days prior to Cycle 1 Day 1) and continually evaluate toxicities past the DLT evaluation period.

Safety Lead-in Cohort 1 (28-Day Cycle):

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

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

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

If ≥2 of the 6 evaluable subjects in Safety Lead-in Cohort 1 experience a DLT (as defined in Section 6.6.1.1, either De-escalation Cohort 1a or 1b could be explored based on the toxicity.

In Cohort 1a, 6 subjects will receive the following combination regimen:

- TTX-030 (40 mg/kg 7 days prior to Cycle 1 Day 1 followed by 20 mg/kg Q2W)
- Budigalimab (500 mg Q4W)
- mFOLFOX6 - **Note:** A change to mFOLFOX6 (i.e., dose reduction or combination modification) may be permitted if the Cohort Review Committee determines that a potential DLT is a known chemotherapy-related toxicity. If a known 5-FU or oxaliplatin toxicity occurs, the relevant drug should be dose reduced; 5-FU should be dose reduced prior to oxaliplatin.

If ≥2 of the 6 evaluable subjects in De-escalation Cohort 1a experience a DLT, budigalimab based on the safety profile and preliminary antitumor activity, Cohort 1b with a doublet combination of TTX-030 and budigalimab or an alternative triplet combination of TTX-030, budigalimab, and mFOLFOX6 may be explored either after Cohort 1a or after the Safety Lead-in after review of the available safety and PK data. The proposed doublet and triplet combination regimens may include:

Doublet combination regimen:

- TTX-030 (40 mg/kg 7 days prior to Cycle 1 Day 1 followed by 20 mg/kg Q2W)
- Budigalimab (500 mg Q4W)

Triplet combination regimen:

- TTX-030 (30 mg/kg 7 days prior to Cycle 1 Day 1 followed by 20 mg/kg Q2W)
- Budigalimab (500 mg Q4W)
- mFOLFOX6 - **Note:** A change to mFOLFOX6 (i.e., dose reduction or combination modification) may be permitted if the Cohort Review Committee determines that a potential DLT is a known chemotherapy-related toxicity. If a known 5-FU or oxaliplatin toxicity occurs, the relevant drug should be dose reduced; 5-FU should be dose reduced prior to oxaliplatin.

Safety Lead-in Cohort 2 (21-Day Cycle):

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

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

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

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

- TTX-030 (40 mg/kg 7 days prior to Cycle 1 Day 1 followed by 30 mg/kg Q3W)
- Budigalimab (375 mg Q3W)
- Docetaxel (60 mg/m^2 Q3W)

If ≥2 of the 6 evaluable subjects in De-escalation Cohort 2a experience a DLT, based on the safety profile and preliminary antitumor activity, Cohort 2b with a doublet combination of TTX-030 and budigalimab or an alternative triplet combination of TTX-030, budigalimab, and docetaxel may be explored either after Cohort 2a or after the Safety Lead-in after review of the safety and PK data. The proposed doublet and triplet combination regimens may include:

Doublet combination regimen:

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

Triplet combination regimen:

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

The study may be stopped early if any doses are considered unsafe. Conversely, the study may be stopped early for having sufficiently characterized the maximum tolerated dose if at least 6 subjects enrolled in each Safety Lead-in cohort have completed the DLT evaluation period. After the safe dose level of TTX-030 combination therapy has been identified, a comparable fixed dose could be explored in a safety lead-in type design.

4.1.1.2 Expansion Phase

The Expansion Phase includes 6 cohorts, as described below. Multiple expansion cohorts may enroll in parallel. The Sponsor may choose not to open 1 or more of the Expansion cohorts. Expansion of up to 40 subjects in select cohorts will be allowed based on review of safety, efficacy, and statistical considerations by the Sponsor and Cohort Review Committee, see Section 4.1.2 and Section 9.4. Cohorts 5, 6, and 7 were removed/discontinued under Amendment 3, Version 4 of the protocol. Subjects who were screened or enrolled into any of the discontinued cohorts prior to cohort termination will continue on study as per protocol.

Expansion Cohorts 3 and 12 (28-Day Cycle)

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

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

Expansion Cohorts 4, 6, 8, and 10 (21-Day Cycle)

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

- Expansion Cohort 4: Metastatic CRC that is known to be microsatellite stable and has previously been treated with up to 3 prior systemic chemotherapy regimens for metastatic disease.
- Expansion Cohort 5: [Cohort removed under Amendment 3, Version 4.0].
- Expansion Cohort 6: Recurrent/metastatic HNSCC after progression on immune checkpoint inhibitors (anti-PD-[L]1) primary or secondary resistant. Subjects may have received up to 3 lines of prior systemic therapies for recurrent/metastatic disease. [Cohort enrollment discontinued under Amendment 3, Version 4.0].

- Expansion Cohort 7: [Cohort enrollment discontinued under Amendment 3, Version 4.0].
- Expansion Cohort 8: Advanced unresectable or metastatic adenocarcinoma of the stomach or gastroesophageal junction, previously treated with up to 3 prior systemic therapy regimens for metastatic disease, and anti-PD-L1 naive.
- Expansion Cohort 10: Unresectable or metastatic urothelial cell carcinoma ineligible a) any platinum-containing chemotherapy regardless of PD-L1 status **OR** b) received prior (neo-)adjuvant platinum-containing with disease recurrence >12 months since completion of therapy.

Expansion Cohorts 9 and 11 (28-Day Cycle)

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

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

4.1.2 Cohort Review Committee

The Cohort Review Committee is composed of study Investigators, the Sponsor's Medical Monitor (or qualified delegate), with ad hoc participation from other members such as the biostatistician, as applicable.

A review of the safety data for the Safety Lead-in Cohorts will be conducted by the Cohort Review Committee. Subsequent de-escalation cohorts will not be dosed until safety data from the study treatment period are obtained from subjects in the current cohort. The Cohort Review Committee will be fully aware of clinical and laboratory data and will determine whether dose de-escalation is appropriate in the Safety Lead-in stage of the study. Safety will be evaluated based on AEs, clinical laboratory test results, and other relevant clinical findings observed during the study treatment period. PK and pharmacodynamic data that are available will also be reviewed, although these are not required to make a dose-finding decision.

Cohort Review Committee evaluations will determine whether a DLT has occurred. The Cohort Review Committee will be made aware of all safety data across all cohorts and both arms. The Cohort Review Committee may choose to apply safety knowledge gained from one arm to more conservatively manage the other arm.

Any toxicity occurring within an earlier cohort after formal Cohort Review Committee review will be reviewed by the Cohort Review Committee along with safety data from the current cohorts and used to make decisions regarding further cohort expansion or dose modification.

For the first 6 subjects to reach Cycle 2 Day 1 in Expansion Cohort 9, a review of the safety experience on treatment will be conducted. The safety review will analyze whether unacceptable toxicities attributable to TTX-030 were observed. If unacceptable toxicities attributable to

TTX-030 will occur in ≥2 of the first 6 subjects, then an alternate cohort design will be considered.

4.2 Rationale for Study Design

Based on preliminary data from this current study, TTX-030 has been combined with budigalimab and mFOLFOX6 with no emerging safety signals beyond what would be expected with mFOLFOX6 alone. TTX-030 in combination with pembrolizumab or gemcitabine + nab-paclitaxel has been evaluated in Study TTX-030-001 (see Section 2.2.2.2.1). The combinations of TTX-030 plus budigalimab and/or mFOLFOX6 were explored in this Phase 1/1b study, which included a safety lead-in and expansion phase, in subjects with advanced solid tumors (see Section 4.1.1 for study design details). The Safety Lead-in identified the doses of TTX-030, budigalimab, and mFOLFOX6 to be evaluated in the Expansion Phase. The TTX-030 RP2D has been successfully identified in combination with budigalimab and mFOLFOX6. The Expansion Phase will further evaluate the activity of TTX-030 in combination with pembrolizumab or budigalimab and/or chemotherapy in subjects with selected advanced solid tumors.

Based on the FDA approval of nivolumab in combination with select types of chemotherapy for the treatment of patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma, subjects will no longer be randomized to Cohort 3 Arm A. Effective 1 Jun 2021, all new subjects eligible for Cohort 3 will only enroll in Arm B.

4.3 Justification for Dose

4.3.1 Rationale for TTX-030 Dose and Schedule

Based on the current PK, receptor occupancy data and safety from the ongoing first-in-human Phase 1 study (TTX-030-001) that is evaluating TTX-030 as monotherapy and in combination with other agents in subjects with advanced solid tumor malignancies or lymphoma, a RP2D was determined to be a 40 mg/kg loading dose 7 days prior to Cycle 1 Day 1 and then either 30 mg/kg Q3W or 20 mg/kg Q2W.

As of the clinical data cut-off date of 10 January 2020, doses of TTX-030 monotherapy up to 40 mg/kg Q3W have been evaluated in Study TTX-030-001 and demonstrated to be well tolerated. No DLTs have been reported (Section 2.2.2.2).

PK demonstrated that a dose of 40 mg/kg Q3W achieved a minimal functional trough level based on activity of TTX-030 in preclinical human functional assays (i.e., enhancement of IL-2 from PBMCs and inflammasome activation). Clearance appears to be independent of dose at doses ≥6 mg/kg, suggesting linear or dose-proportional PK. The half-life was 18.9 days. After the completion of the dose escalation portion of the study, the totality of the PK data was used for PK modeling for the RP2D. Based on the simulations, it was determined that a loading dose of 40 mg/kg one week prior to Cycle 1, Day 1 dosing of 30 mg/kg Q3W or 20 mg/kg Q2W will provide a minimal functional trough level in greater than 80% of patients before Cycle 1, Day 1 and in cycles thereafter.

In the 0.5, 1.5, 3.0, 6.0, 10.0, and 20.0 mg/kg Q3W dose groups, receptor occupancy data demonstrated that doses greater than or equal to 6 mg/kg achieved and maintained higher levels

of peripheral blood receptor occupancy through 21 days post-Cycle 1 on $CD39^+$ monocytes, B cells, and regulatory T cells. At doses ≤3 mg/kg, receptor occupancy levels were lower and decreased 7-14 days post-Cycle 1.

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

4.3.2 Rationale for Budigalimab Dose and Schedule

Based on the observed safety, PK, pharmacodynamics, and efficacy data, the RP2D was determined to be flat doses of 250 mg Q2W, 375 mg Q3W, or 500 mg Q4W. The RP2D was also supported by population PK modeling and simulations that indicated the exposures achieved with 250 mg Q2W, 375 mg Q3W, or 500 mg Q4W doses would result in saturation of PD-1 positive CD4 central memory T-cells and significant PD-L1 blockade, with no further impact on safety (Powderly et al, 2018).

4.3.3 Rationale for mFOLFOX6 Dose and Schedule

mFOLFOX6 will be administered based on standard clinical practice (oxaliplatin 85 mg/m^2 IV with leucovorin 400 mg/m^2 IV over 2 hours plus 5-FU 400 mg/m^2 IV bolus and 2400 mg/m^2 continuous infusion over 46 hours, administered Q2W).

As described in Section 4.1.1.1, a change to mFOLFOX6 (i.e., dose reduction or combination modification) may be permitted according to institutional guidelines.

4.3.4 Rationale for Docetaxel Dose and Schedule

Docetaxel will be administered 75 mg/m^2 Q3W as a 1-hour intravenous infusion based on standard clinical practice. As described in Section 4.1.1.1, dose reduction of docetaxel may be permitted according to institutional guidelines.

4.3.5 Rationale for Gemcitabine plus nab-Paclitaxel Dose and Schedule

Gemcitabine 1000 mg/m^2 + nab-paclitaxel 125 mg/m^2 will be administered on Days 1, 8, and 15 every 28-day cycle based on standard clinical practice. Dose modifications are allowed for gemcitabine 1000 mg/m^2 + nab-paclitaxel 125 mg/m^2 if due to toxicity or intolerability (e.g., Days 1 and 8 or Days 1 and 15 each every 28-day cycle) or according to institutional guidelines).

4.3.6 Rationale for Pembrolizumab Dose and Schedule

Pembrolizumab 200 mg Q3W is based on standard clinical practice. For dose modifications, see KEYTRUDA PI, 2020.

4.4 End-of-Study Definition

The end of this study is defined as the date when the last visit of the last subject occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last subject, whichever occurs later.

The total length of the study, from screening of the first subject to the end of the study, is expected to be approximately 3 years or based on the Sponsor's decision regardless of the reason for closing the trial before the 3 years are completed.

5 STUDY POPULATION

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

5.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all of the general inclusion criteria and relevant disease-specific inclusion criteria below apply.

General Inclusion Criteria

1. Capable of giving signed informed consent as described in Section 10.4, 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 only: ≥19 years of age at the time of screening).
3. Fresh and/or archival tumor tissue (archival tissue can be used if collected within 90 days prior to first dose as long as **there has been no intervening therapy**) is mandatory for all subjects unless clinically contraindicated (see also Section 8.8). For mCRPC subjects, a bone biopsy may be collected if it is unsafe to perform a soft-tissue biopsy or the subject has bone-only disease and bone lesions do not have a soft-tissue component.
4. For combination study treatment that includes budigalimab (ABBV-181), subject must weigh ≥35 kg.
5. Evidence of measurable disease, except for mCRPC (Expansion Cohort 7), by computed tomography (CT), CT-positron emission tomography (PET), or magnetic resonance imaging (MRI) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
6. Life expectancy >12 weeks.
7. Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 (see Appendix 1). NOTE: Subjects eligible for Cohort 10 may have an ECOG score of 2 after approval by the Medical Monitor.
8. Adequate organ and marrow function, as defined below:
    a. Absolute neutrophil count ≥1.5 k/µL, platelets ≥75 k/µL (platelets ≥100 k/µL for chemotherapy arms), hemoglobin ≥8 g/dL (hemoglobin ≥9 g/dL for chemotherapy arms). NOTE: Prior red blood cell or platelet transfusion is allowed if it occurred >2 weeks prior to first dose.
    b. Serum creatinine ≤1.5 x upper limit of normal (ULN) or creatinine clearance (CrCl) ≥40 mL/min. NOTE: Subjects eligible for Cohort 10 may have CrCl <40 mL/min after approval by the Medical Monitor.
    c. Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤2.5 x ULN (or ≤5 x ULN with hepatic metastases)
    d. Total bilirubin ≤2 x ULN (or ≤3 x ULN with Gilbert's syndrome)

e. Prothrombin time (PT)/international normalized ratio (INR) and activated partial thromboplastin time (aPTT) ≤1.2 x ULN; fibrinogen ≥150 mg/dL

f. Serum albumin ≥3.0 g/dL

9. At least 14 days since last dose of chemotherapy or biological therapy or tyrosine kinase inhibitor or high-dose (e.g., >10 mg prednisone or equivalent per day) steroid therapy prior to the loading dose/first dose of study treatment or other second-generation hormone therapy prior to the loading dose/first dose of study treatment.
10. Resolution of adverse effects 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). NOTE: Subjects eligible for Cohort 10 may have Grade ≥2 peripheral neuropathy after approval by the Medical Monitor.
11. Women of childbearing potential and all men must agree to use highly effective methods of contraception through 150 days after the last administration of 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; and oral, injected, or implanted hormonal contraception AND barrier methods of contraception. (Prescribing information should be followed if different from the above.)
12. Subjects with history of congestive heart failure must have cardiac echocardiogram or multigated acquisition scan indicating left ventricular ejection fraction ≥45% within 21 days prior to the loading dose/first dose of study treatment.

Disease-specific Inclusion Criteria

Safety Lead-in Cohort 1

13. Histologically confirmed diagnosis of unresectable or metastatic solid tumor malignancy that has not been treated previously and eligible for mFOLFOX6.
14. Subjects who experienced Grade 1-2 immune-related AEs (irAEs) during prior anti-PD-(L)1 therapy must have documentation that their irAEs improved to Grade ≤1 or baseline **and** subjects must be off steroid therapy and/or other immunosuppressive therapy, as treatment for irAEs, for ≥30 days.
15. Subjects who experienced Grade 3 irAEs consisting of laboratory abnormalities that were asymptomatic and have now resolved to Grade ≤1 or baseline **and** subjects who have been off steroid and/or other immunosuppressive therapy, as treatment for irAEs, for ≥30 days will be able to participate in the study.

    a. No history of Grade ≥3 pneumonitis or any Grade 4 toxicity during prior anti-PD-(L)1 therapy.

    b. No history of Grade ≥2 neuropathy or ocular or cardiac toxicity.

Expansion Cohorts 3 and 12

16. Histologically or cytologically confirmed diagnosis of advanced unresectable or metastatic adenocarcinoma of the stomach or gastroesophageal junction with HER2-negative disease

(HER2 0 or 1 by IHC or HER2 2+ by IHC and no HER2 gene amplification by in situ hybridization [ISH]).

17. Subjects must have histologically or cytologically confirmed HER2-negative disease (HER2 0 or 1 by IHC or HER2 2+ by IHC and no HER2 gene amplification by ISH) on primary or metastatic tumor.
18. No prior treatment for metastatic disease, and no prior (neo-)adjuvant therapy within 6 months of study enrollment.

Expansion Cohort 4

19. Histologically confirmed adenocarcinoma originating from the colon or rectum (stage IV American Joint Committee on Cancer 8th edition) that is known to be microsatellite stable.
20. Experienced disease progression or was intolerant up to 3 prior systemic chemotherapy regimens for metastatic CRC. Prior regimens must have included a 5-fluoropyrimidines based regimen; adjuvant regimen can be considered as one chemotherapy regimen for metastatic disease if the subject had disease recurrence within 6 months of completion; disease progression must have occurred within 3 months of the last systemic therapy administration.

Expansion Cohort 5 (Removed)

[This cohort was removed under Amendment 3, Version 4.0.]

Expansion Cohort 6 (Discontinued)

21. Histologically or cytologically confirmed diagnosis of recurrent or metastatic HNSCC of the oral cavity, oropharynx, hypopharynx, and larynx.
22. Up to 3 lines of prior systemic therapies for recurrent or metastatic disease.
23. Subjects must have progressed on or after an immune checkpoint inhibitor (anti-PD-[L]1) that can be either primary or secondary resistant.
24. HPV status to be known or obtained prior to dosing.

Safety Lead-in Cohort 2 and Expansion Cohort 7 (Cohort 7 Discontinued)

25. Histologically or cytologically confirmed adenocarcinoma of the prostate.
26. Serum testosterone levels less than 50 ng/dL while receiving continued androgen-deprivation therapy.
27. Radiographic evidence of metastatic disease and disease progression (PSA progression per Prostate Cancer Working Group [PCWG3] definition) on the recent prior systemic regimen. Bone only disease is acceptable if the subject meets progression based on PCWG3. The subject must also be willing to provide prior PSA results.
28. Subjects must have received at least 1 prior second-generation anti-androgen therapy (e.g., enzalutamide, abiraterone) approved for mCRPC and have not received docetaxel in the mCRPC setting and are eligible for docetaxel.

Expansion Cohort 8

29. Histologically or cytologically confirmed diagnosis of advanced unresectable or metastatic adenocarcinoma of the stomach or gastroesophageal junction.

30. Up to 3 lines of prior systemic therapies for recurrent or metastatic disease.
31. Subjects must be anti-PD-(L)1 naïve.

Expansion Cohorts 9 and 11

32. Histologically or cytologically confirmed diagnosis of locally advanced, unresectable, or metastatic pancreatic adenocarcinoma.
33. Naïve to any prior treatment for metastatic disease. Prior (neo-)adjuvant therapy is permitted if it was completed at least 6 months prior to study enrollment.
34. Eligible to receive gemcitabine + nab-paclitaxel as standard of care.

Expansion Cohort 10

35. Diagnosis of unresectable or metastatic UCC.
36. Subject must meet at least one of the following criteria:
    a) Subject is ineligible for any platinum-containing chemotherapy

    OR

    b) Subject experienced disease progression within 12 months of (neo-)adjuvant treatment with platinum-containing therapy

5.2 Exclusion Criteria

Subjects are excluded from the study if any of the general exclusion criteria and relevant cohort-specific exclusion criteria below apply.

General Exclusion Criteria

1. History of allergy or hypersensitivity to planned study treatment components. Subjects with a history of severe hypersensitivity reaction to any monoclonal antibody (defined as any Grade 3 reaction lasting ≥48 hours despite optimal therapy) are excluded.
2. Use of investigational agent within 14 days prior to the loading dose/first dose of study treatment and throughout the study.
3. Subject has received anticancer therapy including chemotherapy, radiation therapy, biologic therapy, herbal therapy, or any investigational therapy within 14 days prior to the loading dose/first dose of study treatment. Palliative radiation therapy to non-target lesions is allowed.
4. Subject has received high-dose (e.g., >10 mg prednisone or equivalent per day) systemic steroid therapy or any other form of immunosuppressive therapy within 14 days prior to the loading dose/first dose of study treatment. NOTE: Inhaled, intranasal, intraocular, topical, and intraarticular steroids are allowed. Transient steroid administration as anti-emetic or chemotherapy pre-conditioning (e.g., for paclitaxel) is allowed per institutional guidelines.
5. Subject is receiving therapeutic anticoagulation. NOTE: *Prophylactic* anticoagulation with low-molecular-weight heparin, Factor Xa inhibitors, and low-dose aspirin is allowed.
6. History of autoimmune disease (e.g., rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease) requiring systemic treatment or transplant that requires systemic

steroids or immunosuppressive agents within the last 2 years. NOTE: History of vitiligo, autoimmune thyroiditis, or mild psoriasis is allowed.

7. Known history of HIV or other chronic immunodeficiency.
8. Uncontrolled intercurrent illness including, but not limited to:
    a. Uncontrolled diabetes.
    b. Ongoing or active bacterial, viral, or fungal infection requiring systemic treatment.
    c. Clinically significant congestive heart failure defined by New York Heart Association Class 3 or Class 4.
    d. Unstable angina, arrhythmia, or myocardial infarction within 6 months prior to screening.
    e. Uncontrolled tumor-related pain. Subjects requiring narcotic pain medication must be on a stable regimen at study entry.
    f. Poorly controlled hypertension, defined as a blood pressure consistently above 150/90 mmHg despite optimal medical management.
    g. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring repeated drainage more than once every 28 days. Indwelling drainage catheters (e.g., PleurX®) are allowed.
    h. Active or chronic viral hepatitis B or C infection. Subjects who are positive for hepatitis B surface antigen or hepatitis C antibody are excluded. If hepatitis B core antibody is positive, the subject must have a negative PCR result before enrollment. Those who are PCR positive will be excluded.
    i. Uncontrolled thyroid disease.
    j. Known history of active tuberculosis.
    k. Active infection requiring systemic therapy (Grade ≥2) for more than 3 days within 1 week of dosing
9. Active or untreated central nervous system metastases. Subjects with brain metastases are eligible provided they have shown clinical and radiographic SD for at least 4 weeks after definitive therapy and have not used steroids (>10 mg/day of prednisone or equivalent) for at least 4 weeks prior to the loading dose/first dose of study treatment.
10. History of any other malignancy within the past 3 years except for successfully treated non-melanoma skin cancer or localized carcinoma in situ that is considered cured or adequately treated by the Investigator. Note: Subjects with completely resected cutaneous melanoma (early stage), basal cell carcinoma, cutaneous squamous cell carcinoma, cervical carcinoma in-situ, breast carcinoma in-situ, and localized prostate cancer are eligible.
11. Women who are pregnant or breastfeeding.
12. Subject has received live vaccine within 28 days prior to the loading dose/first dose of study drug.
13. History of (except in the setting of PD-(L)1 therapy) or ongoing pneumonitis or interstitial lung disease and history of idiopathic pulmonary fibrosis, organizing pneumonia, bronchiolitis obliterans, drug-induced pneumonitis, or idiopathic pneumonitis.

14. Subjects who have been previously treated with an anti PD-(L)1 targeting agent must not have had the following during the course of their therapy:
    a. Any immune-mediated toxicity of Grade 3 or worse severity.
    b. Any ocular or neurologic toxicity.
    c. Any hypersensitivity to PD-(L)1 targeting agents for subjects in the budigalimab (ABBV-181) and pembrolizumab-containing cohorts.
15. Subject is judged by the Investigator to have evidence of ongoing hemolysis on hemolysis panel (total, direct and unconjugated serum bilirubin, peripheral blood smear, D-dimers, and serum haptoglobin).
16. Subject has had major surgery per the Investigator within 28 days prior to the loading dose/first dose of study drug, and the surgical wound is not fully 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.
17. History of major immunologic reaction (Grade 3-4) to any IgG-containing agent.
18. History of primary immunodeficiency, bone marrow transplantation, chronic lymphocytic leukemia, solid organ transplantation, or previous clinical diagnosis of tuberculosis.
19. History of Stevens-Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN), or drug reaction with eosinophilia and systemic symptoms (DRESS).

Cohort-specific Exclusion Criteria

Safety Lead-in Cohort 1 and Expansion Cohorts 3 and 12

20. Unable to receive a port or peripherally inserted central catheter.
21. Known hypersensitivity to 5-FU, oxaliplatin, or other platinum agents.
22. Known hypersensitivity to mFOLFOX6 or any of its excipients.
23. Known dihydropyrimidine dehydrogenase deficiency (testing not required).
24. Baseline peripheral neuropathy/paresthesia Grade >1.

Safety Lead-in Cohort 2 and Expansion Cohort 7 (Cohort 7 Discontinued)

25. Known hypersensitivity reactions to polysorbate 80 or an agent contains polysorbate 80.

5.3 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently entered/enrolled 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 MEDICINAL 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 IMP.

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, oxaliplatin, leucovorin, fluorouracil, docetaxel, nab-paclitaxel, and gemcitabine are considered as NIMP and will be supplied locally by the trial sites. Pembrolizumab is also considered as NIMP and will be sourced by either the Sponsor or locally by trial sites.

6.1 Investigational Medicinal Product Description and Administration

The IMPs and NIMPs to be administered in this study are summarized in Table 6 and Study Treatments by Cohort are summarized in Table 7. 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 6: Product Descriptions

Investigational Product Name	Dosage Formulation	Dosage Level/ Potency	Dose Frequency	ROA	Sourcing	Product Status
TTX-030	Aqueous solution	40 mg/kg load, followed by 30 mg/kg Q3W or 20 mg/kg Q2W	Q2W, Q3W	IV infusion	Sponsor	Experimental (IMP)
Budigalimab (ABBV-181)	Powder for solution for infusion	375, 500 mg	Q3W, Q4W	IV infusion	Sponsor	Experimental (IMP)
Oxaliplatin	Aqueous solution	85 mg/m^2	Q2W	IV infusion	Source Locally	Approved cancer therapy (NIMP)
Leucovorin	Lyophilized powder for injection	400 mg/m^2	Q2W	IV infusion	Source locally	Approved cancer therapy (NIMP)
Flourouracil (5-FU)	Aqueous solution	400 mg/m^2	--	Bolus IV	Source Locally	Approved cancer therapy (NIMP)
		2400 mg/m^2	Continuous 46-hour infusion on Days 1 and 2			
Docetaxel	Single-use vial as a sterile, pyrogen-free, nonaqueous solution	75 mg/m^2	Q3W	IV infusion	Source Locally	Approved cancer therapy (NIMP)
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)
		100 mg/m^2	Days 1, 8, and 15 of each 21-day cycle			
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)
Pembrolizumab	Solution for injection	200 mg	Q3W	IV infusion	Sponsor or Source Locally	Approved cancer therapy (NIMP)

IMP=investigational medicinal product; IV=intravenous; NIMP=non-investigational medicinal product; Q2W=every 2 weeks; Q3W=every 3 weeks; Q4W=every 4 weeks; ROA=route of administration; RP2D=recommended Phase 2 dose.

Study treatments by cohort, including length of cycle and route/duration of study, are summarized in Table 7.

Table 7: Study Treatments by Cohort

Study Treatment(s)	Cohort	Cycle	Route/Duration
TTX-030 (Load+Q2W) + Budigalimab (Q4W) + mFOLFOX6 (Q2W)	1 and 3 (Arm B)	28-day	IV over at least 60 minutes for TTX-030 and budigalimab; IV over 48 hours for mFOLFOX6 (may require overnight stay)
TTX-030 (Load+Q2W) + mFOLFOX6 (Q2W)	3 (Arm A)	28-day	IV over at least 60 minutes for TTX-030; IV over 48 hours for mFOLFOX6 (may require overnight stay)
Budigalimab (Q4W) + mFOLFOX6 (Q2W)	12	28-day	IV over at least 60 minutes for budigalimab; IV over 48 hours for mFOLFOX6 (may require overnight stay)
TTX-030 (Load+Q3W) + Budigalimab (Q3W) + Docetaxel (Q3W)	2	21-day	IV over at least 60 minutes for TTX-030 and budigalimab; administer per SOC for approved agent
TTX-030 (Load+Q3W) + Budigalimab (Q3W)	4, 6, and 8	21-day	IV over at least 60 minutes for TTX-030 and budigalimab
TTX-030 (Load+Q2W) + Budigalimab (Q4W) + Gemcitabine + Nab-paclitaxel (Days 1, 8, 15)	9	28-day	IV over at least 60 minutes for TTX-030 and budigalimab; administer per SOC for approved agents
TTX-030 (Load+Q2W) + Gemcitabine + Nab-paclitaxel (Days 1, 8, 15)	11	28-day	IV over at least 60 minutes for TTX-030; administer per SOC for approved agents
TTX-030 (Load+Q3W) + Pembrolizumab (Q3W)	10	21-day	IV over at least 60 minutes for TTX-030; administer per SOC for approved agent

IMP=investigational medicinal product; IV=intravenous; Q2W=every 2 weeks; Q3W=every 3 weeks; Q4W=every 4 weeks; SOC=standard of care.

Note: IMP treatments are administered in the order listed, with a minimum of 60 minutes wait time between infusions. TTX-030 may be infused less than 60 minutes for 20 mg/kg dosing days depending on weight. Refer to IMP Manual for details.

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 product 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.

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

6.2 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 product, and only authorized site staff may supply or administer investigational product. 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 investigational product accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused investigational products are provided in the Study Pharmacy Manual.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Investigational Product Assignment and Randomization

All treatment assignments of subjects may be done using an Interactive Response Technology upon enrollment confirmation by the Sponsor or designee. Subjects in Expansion Cohort 3 were randomized (as described in Section 4.1.1.2) prior to implementation of Amendment 4, Version 5.0, which discontinued Arm A. A separate instruction manual will be provided to each site. A subject is considered entered into the study once the Investigator (or designee) confirms eligibility and notifies the Sponsor that the subject is enrolled in the study.

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 Blinding

This is an open-label trial; therefore, the Sponsor, Investigator, and subject will know the investigational product administered.

6.4 Investigational Product Compliance

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

6.5 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.

6.5.1 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, Factor Xa inhibitors, and low-dose aspirin are allowed. Low-dose aspirin is permitted, but it is advisable for subjects to switch to low-molecular-weight heparin.

For subjects enrolled in Cohort 2, premedication regimen is to be administered as indicated in the label approved for docetaxel in the applicable country in order to minimize severe hypersensitivity reactions and fluid retention that may occur after docetaxel administration.

6.5.2 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:

- Steroids are not permitted. Inhaled, intranasal, intraocular, topical, and intra-articular steroids are allowed. Transient steroid administration is allowed as anti-emetic or chemotherapy pre-conditioning (e.g., mFOLFOX regimen) per institutional guidelines.
- Immunosuppressive medications, including chronic systemic corticosteroids at greater than physiologic doses (a dose of 10 mg/day oral prednisone or equivalent) 14 days before the loading dose/first dose (except for subjects who require hormone replacement therapy such as hydrocortisone). 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 solid tumors, including immunotherapy, chemotherapy, and radiation therapy. NOTE: Palliative radiation may be allowed during the trial on a case-by-case basis – please discuss with the 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 Sponsor. 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.

6.6 Treatment Modifications

For the Safety Lead-in stage, dose-finding decisions will be made by the Cohort Review Committee based on safety data. The Cohort Review Committee will determine whether a DLT has occurred (Section 6.6.1).

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 6.6.2 and Section 6.6.3.

Safety risks associated with budigalimab, mFOLFOX6, docetaxel, gemcitabine + nab-paclitaxel and pembrolizumab and recommendations for managing these risks are described in Section 6.6.2.

6.6.1 Treatment Modifications for Dose-limiting Toxicity

6.6.1.1 Definition of a Dose-limiting Toxicity

A DLT is defined as the occurrence of any of the following toxicities within the DLT treatment period if judged by the Investigator and Sponsor to be possibly, probably, or definitely related to TTX-030 or budigalimab:

- Any febrile neutropenia
- Grade ≥3 thrombocytopenia with clinically significant hemorrhage
- Grade ≥3 non-hematologic AEs, except the following:
  - Grade ≥3 nausea, vomiting, or diarrhea lasting <72 hours in the absence of maximal medical therapy

  - Grade ≥3 abnormal laboratory values that are not clinically significant and corrected within 72 hours
  - Grade ≥3 fatigue lasting <5 days
  - Grade 3 AST and ALT elevations lasting <7 days
  - Grade 3 non-hepatic-related increases in alkaline phosphatase will not be considered a DLT
- AST or ALT >3 x ULN (>2 x baseline AND >3 x ULN in subjects with baseline elevation) AND total bilirubin >2 x ULN (>2 x baseline AND >2 x ULN in subjects with baseline elevation) or clinical jaundice, without initial findings of cholestasis AND no other immediately apparent identifiable possible causes of elevated liver enzymes and hyperbilirubinemia (criteria meeting Hy's law)

Safety data will be evaluated by the Cohort Review Committee (described in Section 4.1.2). Laboratory abnormalities that are asymptomatic and deemed not clinically significant will not be regarded as a DLT, unless specified above.

The toxicity must either return to the baseline level at which the subject was enrolled or to Grade 1 or less prior to subsequent administration of TTX-030 or budigalimab combination and must be agreed upon in writing with the Medical Monitor.

If an AE does not meet the DLT criteria but is deemed clinically significant and one that can require a change in the dosing interval, then the Investigator is asked to contact the Medical Monitor to develop a subject management plan.

6.6.2 Treatment Modifications for TTX-030 Combined with Pembrolizumab or Budigalimab and/or Chemotherapy

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. If a toxicity does not resolve or the criteria for resuming study drug are not met, the subject must be discontinued from the agent(s) to which the toxicity is attributed. Holding of 1 agent and not the other agent 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 with pembrolizumab or budigalimab and/or chemotherapy (e.g., mFOLFOX6 or docetaxel, gemcitabine + nab-paclitaxel), as well as the measures taken to avoid or minimize such toxicity in this study, are described in the following sections.

6.6.2.1 Management of Toxicities Associated With TTX-030

Based on currently available data, TTX-030 has shown a favorable safety profile when administered as monotherapy. During the monotherapy dose escalation portion of the first-in-human Study TTX-030-001, no DLTs were reported, the MTD was not reached, and the RP2D was informed by PK and PD observations. Various safety lead-in cohorts of Study

TTX-030-001 and Study TTX-030-002 also have shown that TTX-030 can be safely combined with checkpoint inhibitors and/or chemotherapy in doublet or triple combinations in absence of excessive or synergistic toxicities (please refer to the current IB for details). Infusion-related reaction, which may occur with biologic products, has been defined as an AE of special interest for TTX-030 (see Table 8 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 (discussion with the Medical Monitor is recommended).
  - If a dose is held for >28 days, TTX-030 may be discontinued permanently (after a discussion with the Medical Monitor).
- For Grade 4-related AEs, dosing of TTX-030 may be discontinued permanently (a discussion with the Medical Monitor is recommended).

6.6.2.2 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 2.2.3.2 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.

6.6.2.3 Management of Toxicities Associated with mFOLFOX6

Toxicities related to mFOLFOX6 are described in the prescribing information (ELOXATIN PI, 2015; LEUCOVORIN PI, 2016; FLUOROURACIL PI, 2017). Dose modifications of mFOLFOX6 may be required in the event of treatment-related toxicity. These guidelines are summarized below (based on ELOXATIN PI, 2015). All toxicities will be graded according to NCI CTCAE v5.0. When in doubt, the Investigator should consult with the Medical Monitor.

Recommended Dose Modifications for mFOLFOX6

Neurosensory events—For subjects who experience persistent Grade 2 neurosensory events that do not resolve, a dose reduction of oxaliplatin to 65 mg/m^2 should be considered. For subjects with persistent Grade 3 neurosensory events, discontinuing oxaliplatin should be considered. The 5-FU/leucovorin regimen need not be altered.

Gastrointestinal and hematologic events—A dose reduction of oxaliplatin to 65 mg/m^2 and 5-FU by 20% is recommended for subjects after recovery from Grade 3/4 gastrointestinal (GI) events (despite prophylactic treatment) or Grade 4 neutropenia or Grade 3/4 thrombocytopenia.

The next dose should be delayed until neutrophil counts are >1.5 x 10^9/L and platelet counts are ≥75 x 10^9/L.

6.6.2.4 Management of Toxicities Associated with Docetaxel

Toxicities related to docetaxel (TAXOTERE) are described in the prescribing information (TAXOTERE PI, 2019). Dose modifications of docetaxel may be required in the event of treatment-related toxicity and managed as per institutional guidelines. All toxicities will be graded according to NCI CTCAE v5.0. When in doubt, the Investigator should consult with the Medical Monitor.

6.6.2.5 Management of Toxicities Associated with Gemcitabine and nab-Paclitaxel

Refer to product labels for management of toxicities (GEMZAR PI 2019, ABRAXANE PI, 2020).

6.6.2.6 Management of Toxicities Associated with Pembrolizumab

Refer to product labels for management of toxicities (KEYTRUDA PI, 2020).

6.6.3 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 8.

Table 8: 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 1.5 hours (±30 minutes) 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. **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.

7 DISCONTINUATIONS OF INVESTIGATIONAL PRODUCT AND SUBJECT STUDY DISCONTINUATION

7.1 Discontinuation of Investigational Product

Treatment with TTX-030-containing regimens may continue for up to 24 months or until disease progression, intolerable toxicity, or death, whichever occurs first. If a subject discontinues any of the combination agents administered with TTX-030, then treatment with the remaining TTX-030-containing regimen may continue if it is well-tolerated. Subjects cannot continue other treatment if TTX-030 is discontinued.

Subjects must discontinue the investigational product(s) if they experience any of the following:

- Unacceptable toxicity related to the investigational product, including the development of DLT, serious adverse event (SAE), or other clinically significant AE or medical conditions, which indicate to the Investigator that continuation of study treatment is not in the best interest of the subject.
- Investigator's decision
- Use of another anticancer therapy
- Pregnancy (see Appendix 7)
- Symptomatic deterioration attributed to disease progression
- Radiographic disease progression

Subjects have the right to voluntarily withdraw from the investigational product at any time for any reason or be dropped from investigational product at the discretion of the Investigator should any untoward effect occur. In addition, a subject may be discontinued from investigational product by the Investigator or Sponsor if investigational product is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

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

The visit at which response assessment shows confirmed progressive disease (PD) per immunotherapy Response Evaluation Criteria in Solid Tumors (iRECIST; Appendix 4) for all solid tumors, except mCRPC, which will be assessed according to PCWG3 (Appendix 5), may be used as the treatment discontinuation visit. Subjects who discontinue investigational product for any reason other than PD or loss of clinical benefit are to continue assessments as outlined in the Schedule of Activities (Section 1.3).

7.2 Subject Discontinuation

When an investigational product is discontinued, subjects should have an end of treatment/discontinuation assessment and continue follow-up assessments as outlined in the Schedule of Activities (Section 1.3). Information on survival follow-up and new anticancer therapy will be collected for all subjects via telephone calls, subject medical records, and/or clinic visits until any of the following occurs:

- Death
- Lost to follow-up
- Study termination by the Sponsor
    - Subject requests to be withdrawn from follow-up. If a subject request 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.
- Investigator requests that the subject is withdrawn from follow-up

In addition, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. However, subjects who withdraw consent will not be followed for any reason after consent has been withdrawn. Subjects who withdraw from the study will not be replaced.

7.3 Follow-up

After completing the end of treatment visit, subjects will enter the post-treatment Follow-up provided they have documented radiographic disease progression at the end of treatment visit. Subjects who withdraw from treatment for reasons other than documented radiographic disease progression will participate in the Efficacy Follow-ups.

7.3.1 Efficacy Follow-up

Subjects who discontinue treatment for reasons other than documented disease progression will continue to have normally scheduled clinical assessments (every 8 weeks [-7 days] 28-day cycle or every 9 weeks 21-day cycle [-7 days]) until disease progression is documented, death, initiation of alternative anticancer treatment, withdrawal of consent for further follow-up, or lost to further follow up.

- Physical examination
- Radiological disease assessments (CT, MRI, bone scans)
- Serum tumor-associated markers (as applicable)

7.3.2 Safety Follow-up

For subjects who discontinue study treatment, have documented disease progression, and have not withdrawn consent for post-treatment follow-up, they (or a partner/relative where appropriate) will be contacted 60 (±7) and 90 (±7) days after the last dose to assess safety and 180 (±15) days after last dose to obtain disease status and/or use of alternative anticancer treatment and survival status.

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 or not the subject wishes to and/or should continue in the study.
- 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 is 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.

8 STUDY ASSESSMENTS AND PROCEDURES

Please see Section 1.3 for the Schedule of Activities to be performed during the study. 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 Principal 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. 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 or not the subject is still receiving treatment) or until the subject comes off study or starts alternative anticancer treatment. At the Investigator's discretion, tumor assessments may be repeated at any time if PD is suspected. Confirmation assessment of PD must be obtained at least 4 weeks after the initial disease assessment indicating PD; this is not applicable to subjects who have started another anticancer therapy.

All subjects who discontinue investigational product for reasons other than disease progression (e.g., AEs) will continue tumor assessments until death, disease progression, initiation of another systemic anticancer therapy, lost to follow-up, withdrawal of consent, or study termination, whichever occurs first.

Measurable and evaluable lesions, as defined by tumor-specific response criteria, should be assessed and documented at screening. Response assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to enrollment do not have to be repeated at screening.

CT/MRI scans of the chest, abdomen, and pelvis are required for all subjects. HNSCC subjects must have CT/MRI scans of the head, neck, and chest. Tumor assessments will include all known or suspected disease sites. Anatomic regions included in the CT/MRI scans should be per disease history and clinical symptoms (repeat the same CT/MRI series for all post-treatment tumor assessments as completed at screening). All scans should be performed in accordance with RECIST v1.1 and with contrast. If contrast is contraindicated (i.e., in subjects with known contrast dye allergy or impaired renal clearance), CT without contrast, MRI, or PET scans will be allowed. The imaging modality used, and anatomic regions assessed must be uniform during study participation. Brain scans and bone scans will be performed at screening if disease is suspected and on study as appropriate to follow disease. Tumor assessment should be repeated at the end of treatment visit if more than 6 weeks (±7 days) have passed since the last evaluation.

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 full contrast diagnostic CT scan.

Response will be assessed by the Investigator using RECIST v1.1 (see Appendix 3) and iRECIST (Appendix 4) for all solid tumors, except mCRPC, which will be assessed according to PCWG3 (Appendix 5), but treatment may continue until confirmation of PD with a repeat scan performed at least 4 weeks from the initial PD assessment. 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. An independent radiology read may be performed for select subjects who respond to study treatment.

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 and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including, stage, date of diagnoses, and prior cancer therapies and procedures), PD-L1 expression, combined positive score (select cohorts), reproductive status, and smoking 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 within 28 days prior to initiation of investigational product will be recorded. Demographic data may include age, sex, and race/ethnicity.

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 ECG recording (all 3 within a 5-minute time period, at least 1 minute apart) will be obtained at screening and during the study as outlined in the Schedule of Activities (Section 1.3). ECGs acquired on different days should be as closely time matched as feasible. Interpretable ECG recordings (e.g., without artifacts) must be obtained at each timepoint.

All ECG recordings must be performed using an institutionally approved ECG machine. Lead placement should be as consistent as possible. ECG recordings must be performed after the subject has been resting in a supine position for at least 10 minutes. 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. Paper copies of ECG tracings will be kept as part of the subject's permanent study file at the site. At a minimum, QTc interval should be recorded on the appropriate eCRF page. Any morphologic waveform changes or other ECG abnormalities must also be documented on the eCRF page.

8.2.5 Clinical Safety Laboratory Assessments

Blood samples for clinical safety laboratory testing will be collected at the timepoints described in the Schedule of Activities (Section 1.3). Safety laboratory tests to be performed are summarized in Table 9.

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 the visit specified in Section 1.3. Visits conducted outside the windows are to be discussed with the Medical Monitor (or designee). On treatment days, samples for clinical laboratory testing should be drawn prior to the infusion.

The Investigator 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 9: Safety Laboratory Tests for Analysis

Profile	Laboratory Test
Hematology[a]	Red blood cell (RBC) count Hemoglobin Hematocrit White blood cell (WBC) count Absolute neutrophils Absolute lymphocytes Absolute monocytes Absolute eosinophils Absolute basophils Platelets
Serum chemistry	Sodium Potassium Chloride Bicarbonate Glucose (non-fasted) Creatinine Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Alkaline phosphatase (ALP) Gamma-glutamyltransferase (GGT) Lactate dehydrogenase (LDH) Total bilirubin Total protein Albumin Blood urea nitrogen (BUN) or urea Total calcium Phosphorus or phosphate Magnesium

Profile	Laboratory Test
	Creatine kinase Uric acid Amylase Lipase C-reactive protein
Other	Serology (screening only): HBV, HCV, HPV (subjects with HNSCC only) Coagulation: PT/INR, PTT, fibrinogen Urinalysis: pH, glucose (qual), protein (qual), blood (qual), ketones, nitrites, leukocyte esterase, urobilinogen, urine bilirubin Pregnancy test (women of childbearing potential only) Hemoglobin A1c (HbA1c) Thyroid tests (TSH, free T3, free T4, thyroid antibody) Pituitary tests (baseline only): ACTH, FSH, LH, GH Testosterone (at baseline for subjects with mCRPC only)

ACTH=adrenocorticotropic hormone; FSH=follicle-stimulating hormone; GH=growth hormone; HBV=hepatitis B virus; HCV=hepatitis C virus; HNSCC=head and neck squamous cell carcinoma; HPV=human papillomavirus; INR=international normalized ratio; LH=luteinizing hormone; mCRPC=metastatic castration-resistant prostate cancer; PT=prothrombin time; PTT=partial thromboplastin time; TSH=thyroid-stimulating hormone.

[a] Hematology may be performed more frequently if clinically indicated.

8.3 Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 6.

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 Adverse Event 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 (see Appendix 6).

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 COVID-19 symptoms) and SAEs will be collected from the time the subject signs informed consent through 90 days after the last administration of study treatment or until initiation of a new systemic anticancer therapy, whichever occurs first. A positive COVID-19 test result will be submitted as an SAE.

Prior to initiation of investigational product, only SAEs related to a protocol-mandated intervention should be reported on the Adverse Event eCRF page. Other medical occurrences that begin before the start of investigational product but after informed consent is obtained will be recorded on the Medical History/Current Medical Conditions section of the eCRF, not the AE section.

The method of recording, evaluating, and assessing causality of an AE and SAE and the procedures for completing SAE reports are provided in Appendix 6. The procedure for transmitting SAE reports is provided in Section 8.3.8.2.

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 6)
- 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 6.

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.

Investigators are not obligated to actively seek AE or SAE after the end of the AE reporting period (defined as 90 days after the last administration of study treatment or until initiation of a new systemic anticancer therapy, whichever occurs first). However, 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 using the Safety Notification Form (within 24 hours of site awareness) and SAE Form or Pregnancy Notification Form, as applicable.

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 and through 150 days after the last dose of study treatment (Cohorts 1-4, 8, 10, and 12). For female subjects of reproductive potential that are receiving gemcitabine and nab-paclitaxel (Cohorts 9 and 11), subjects are advised to continue effective contraception for 180 days after the last dose of 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 150 days after the last administration of 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 7. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

A Pregnancy Notification Form should be completed and submitted to the Sponsor or its designee immediately, either by faxing or by scanning and emailing the form using the fax number or email address provided to Investigators (see Section 8.3.8.2). 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 the 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 Serious 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 have been reported.

8.3.8 Sponsor Contact Information

8.3.8.1 Emergency Medical Contacts

Medical Monitor or Sponsor Contact Information:

Thomas Jahn, MD, PhD
Trishula Therapeutics, Inc.
2268 Westborough Boulevard, Suite 302 #263
South San Francisco, CA 94080
tjahn@trishulatx.com

Telephone No.: +1 650-822-4401 (Office; United States)

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

8.3.8.2 Safety Reporting Contacts

The contact information on the Safety Notification Form should be used when submitting SAE forms as described in Appendix 6 for SAEs and other reportable safety events and in Section 8.3.5 for pregnancies. The Safety Notification Form and applicable supporting documents (e.g., SAE Form) should be completed and submitted to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the event) by faxing (regional fax numbers are provided on the SAE forms) or emailing the SAE form(s) to the Trishula-designated Pharmacovigilance Group at SAEintake@labcorp.com.

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 above (Section 8.3.8.2). Details of signs and symptoms, clinical management, and outcome should be reported, if applicable. Overdoses should also be captured as protocol deviations.

The Monitoring Plan contains a section related to the classification of deviations, and overdoses will be classified in that document. Deviations are to be captured in the deviation log and reviewed on an ongoing basis by the Medical Monitor and Project Manager. 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 for analysis of TTX-030 PK will be collected according to the Schedule of Activities (see Section 1.3). Serum concentrations for TTX-030 will be determined using a validated assay. The PK parameters listed below will be estimated using Phoenix 64 WinNonlin. The PK parameters are listed in Table 10.

Table 10: Serum Pharmacokinetic Parameters to be Computed

AUC	area under the serum concentration curve (AUC)
C_{max}	maximum observed serum concentration
CL	Total serum clearance
$t_{1/2}$	Half-life
V	volume of distribution

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 ADA to TTX-030 will be collected according to the Schedule of Activities (see Section 1.3) and will be determined using a validated assay.

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.

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

8.8 Tumor Biopsies

Subjects enrolled in the safety lead-in and expansion arms will be required to have a site of disease that is safely accessible for biopsy (paired) upon enrollment. A fresh biopsy from an appropriately accessible lesion with sufficient tumor tissue (obtained from core biopsy, excision biopsy, or surgical specimen) is required at screening (any time prior to the first dose) and on-treatment on C2D1 (-7 days). For Cohort 12, a minimum of 6 paired biopsies are mandated.

If the procedure for the tumor biopsy is deemed unsafe or clinically contraindicated, the investigator should have a discussion with Medical Monitor.

If a subject has had a biopsy within 90 days with no intervening lines of therapy prior to the loading dose/first dose of study treatment, the archival tissue can be used for this study (which should be submitted prior to study treatment administration) and the subject does not need to repeat a baseline biopsy.

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

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 will be kept for up to 15 years after the last subject completes the study.

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 in genetic testing, 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).

The data generated from this research are exploratory in nature and are not expected to provide clinically meaningful information. 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. 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 Pharmacodynamics/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.

Subjects who consent to participate in this optional research may withdraw consent to the use of these samples at any time. 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 STATISTICAL CONSIDERATIONS

9.1 Sample Size Determination

Safety Lead-in

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

Expansion Phase

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

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

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

Table 11: Exact 1-Sided 80% CIs from Various Response Rates

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

CI=confidence interval.

9.2 Populations for Analysis

The analysis populations are defined in Table 12.

Table 12: Populations for Analysis

Population	Description
Enrolled Population	All subjects who sign the informed consent form
All Treated Population	All subjects who receive at least 1 dose or any partial dose of study treatment
DLT-Evaluable Population	All subjects who receive 1 infusion during the treatment cycle and have sufficient safety data or experienced a DLT during Cycle 1
Response-Evaluable Population	All treated subjects with measurable disease, as defined by tumor-specific response criteria, at baseline and 1 of the following: 1) at least 1 on-treatment tumor assessment or 2) death
PK Population	All subjects who receive at least 1 dose of study treatment and have, in the opinion of the pharmacokineticist, sufficient data for PK analysis
Immunogenicity Population	All subjects who receive at least 1 dose of study treatment and have available ADA data
Biomarker/Pharmacodynamic Population	All subjects who receive at least 1 dose of study treatment and have available biomarker data

ADA=antidrug antibody; DLT=dose-limiting toxicity; PK=pharmacokinetics.

9.3 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the study populations to be included in the analyses and the procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.3.1 Safety Analyses

The safety analysis will be based on the All-Treated Population, as defined in Table 12. For the arms in Expansion Cohorts 3 and 12, analysis will be performed based on actual treatment received. The incidence of AEs (including DLTs for Safety Lead-in Cohorts 1 and 2), 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 in each tumor cohort 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.

9.3.2 Efficacy Analyses

The efficacy analysis will be based on the Response-Evaluable Population, as defined in Table 12. For the arms in Expansion Cohorts 3 and 12, analysis will be performed based on treatment as assigned. Efficacy analyses for binary and time-to-event endpoints will be based on Investigator assessment according to RECIST v1.1 (Appendix 3) and iRECIST (Appendix 4) for all solid tumors, except mCRPC, which will assessed according to the PCWG3 criteria (Appendix 5). The efficacy endpoints to be analyzed are listed and defined in Table 13.

Table 13: Efficacy Endpoints

Endpoint	Description
Objective response rate	Defined as the percentage of subjects with unconfirmed and confirmed CR or unconfirmed and confirmed PR
Best overall response	Defined as the best response observed at any of the subject's post-baseline assessments
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
Disease control rate	Defined as the percentage of subjects with a best overall response of CR, PR, or SD
Progression-free survival	Measured from the start of investigational product treatment until first documentation of progression or death from any cause, whichever occurs first
Overall survival	Measured from the start of treatment until death due to any cause

CR=complete response; PR=partial response; SD=stable disease.

ORR and disease control rate will be estimated by the proportion of subjects with objective response and disease control, respectively, and their 80% CIs will be estimated using the exact binomial method. Time-to-event endpoints (duration of response, PFS, and OS) will be summarized using the Kaplan-Meier method.

No formal statistical comparisons between the treatment arms of Expansion Cohorts 3 and 12 are planned.

9.3.3 Pharmacokinetic Analyses

The PK analysis will be based on the PK Population, as defined in Table 12. Serum concentrations of TTX-030 and PK parameter values will be tabulated for each subject and each cohort. Summary statistics will be computed for each sampling time and each parameter.

9.3.4 Immunogenicity Analyses

The immunogenicity analysis will be based on the Immunogenicity Population, as defined in Table 12. Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of subjects who develop detectable anti-TTX-030 antibodies. The immunogenicity titer will be reported for samples confirmed positive for the presence of anti-TTX-030 antibodies.

9.3.5 Biomarker/Pharmacodynamic Analyses

The biomarker analyses are exploratory and will be based on the Biomarker/Pharmacodynamic Population, as defined in Table 12. Baseline and changes from baseline in biomarker measures will be summarized. Possible association between changes in biomarker measures of interest and PK exposure will 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.

9.4 Interim Analyses

No formal interim analysis is planned. Review of the safety data for Safety Lead-in Cohorts 1 and 2 are described in Section 4.1.2.

Given the preliminary nature of the assessment of antitumor activity of TTX-030 in combination with pembrolizumab or budigalimab and/or chemotherapy in Expansion Cohorts 4, 8-11, an informal interim analysis will be performed when 14 subjects have been treated in an expansion cohort. A Cohort Review Committee may also be convened, at the discretion of the Sponsor, and may consider the predictive probability at interim. To illustrate, using a prior of Beta (0.2, 0.8), Table 14 characterizes the predictive probability at the informal interim analysis of the true ORR being less than 5%, 13%, 22%, or 30% with 80% confidence at the future final analysis with 23 subjects if the cohort was to be expanded (Lee and Liu, 2008).

Table 14: Predictive Probability Based on Interim Data (80% Confidence)

Cohort Size (n)	Number of Responders	Observed ORR	Prior: Beta (0.2, 0.8)			
			PP of (true ORR <5%)	PP of (true ORR <13%)	PP of (true ORR <22%)	PP of (true ORR <30%)
14	0	0%	90.8%	97.9%	99.9%	100%
	1	7%	0%	54.9%	93.7%	99.5%
	2	14%	0%	0%	63.0%	93.1%
	3	21%	0%	0%	18.3%	68.7%
	4	29%	0%	0%	0%	30.1%

ORR=objective response rate; PP=predictive probability.

Given a sample size of 14 subjects, the probability to observe at least 1 occurrence of AE is 57.0%-77.1% if the true incidence of the respective AE rate is ≥10%.

Any expansion cohort (Cohorts 4, 8-11) may have their maximum sample size increased from 23 to 40 at the discretion of the Sponsor and Cohort Review Committee. This decision will be based upon the needed for the greater precision of estimation the larger sample size allows; for cohorts with promising data likely to result in future study in confirmatory clinical trials.

10 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1 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 the European Union (EU) or European Economic Area will comply with the EU Clinical Trial Directive (2001/20/EC).

10.2 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 IRB/IEC procedures
- 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, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.3 Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are

responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 4.4).

10.4 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.

10.5 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.

10.6 Dissemination of Clinical Study Data

For all clinical trials in subjects involving an investigational product for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in subjects involving an investigational product for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The results of this study may be published or presented at scientific congresses.

10.7 Administrative Structure

This trial will be sponsored and managed by Trishula and its designees. The Sponsor or its designee will provide clinical operations management and medical 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 monitoring; local laboratory ranges may be collected.

10.8 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). 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 10.9) 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.

10.9 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, microfiche, photographic negatives, microfilm or magnetic media, X-rays, 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 10.12.

10.10 Study and Site Closure

The Sponsor or designee reserves the right to close the study site or terminate any cohorts or 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)

10.11 Site Inspections

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, subjects' medical records, and eCRFs. The Investigator will permit national and local health authorities, the Sponsor, or its designee, and the IRBs/IECs to inspect facilities and records relevant to this study.

10.12 Retention of Records

Records and documents pertaining to the conduct of this study and distribution of the investigational product, including signed eCRFs, electronic or paper subject-reported outcomes data (if applicable), signed ICFs, laboratory test results, and medication inventory records, must be retained by the Investigator 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.

10.13 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.

11 SUPPORTING DOCUMENTATION

11.1 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.

11.2 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 6.6).

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 15 below 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 15: 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 6.6. • 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 6.6. • 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.

11.2.1 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 16, and institutional standard support care should also be administered.

Table 16: 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.

11.2.2 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 17. 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, 2018; 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 17: 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 6.6 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, consider administering 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 6.6). • 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.

11.2.3 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. 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, 2018; 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 18.

Table 18: 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 6.6 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 6.6. • 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.

11.2.4 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 19. 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, 2018; Puzanov et al, 2017).

Table 19: 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 6.6. • 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.

11.2.5 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 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 hypothyroidism and other immune-related endocrine AEs (Brahmer et al, 2018; Haanen et al, 2017; NCCN guidelines, 2018; Puzanov et al, 2017).

Table 20: 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 6.6, 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.

11.2.6 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 21.

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, 2018; 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 21: 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.	<u>If worsens:</u> 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.	<u>When symptoms resolve to baseline/subject is clinically stable:</u> 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. <u>If worsens:</u> 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 6.6 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.	<u>When symptoms resolve to baseline/subject is clinically stable:</u> 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. <u>If worsens:</u> 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.

11.2.7 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: ACTH (morning), cortisol level (morning), and metabolic panel (sodium, potassium, bicarbonate/CO2, 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 22.

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, 2018; Puzanov et al, 2017).

Table 22: 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 6.6 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 Institute Additional 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.

11.2.8 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 23.

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, 2018; Puzanov et al, 2017).

Table 23 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 6.6 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 disease is ready to be discontinued.
- For long-term exposure, consult endocrinology for recovery and weaning protocol using hydrocortisone.

11.2.9 Diabetes Management Algorithm

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

Diabetes management guidelines are provided in Table 24.

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, 2018; Puzanov et al, 2017).

Table 24: 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 type2 diabetes. • Screen for type 1 diabetes if appropriate, for example, acute onset with prior normal values or clinical concern for ketosis. • Consider endocrinology consultation.	If worsens: 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.	If worsens: Treat as Grade 3 – 4. When subject is clinically stable: 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 6.6 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.

11.2.10 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 25. 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 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, 2018; Puzanov et al, 2017).

Table 25: 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 6.6. • 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 6.6. • 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 after3 days, 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 6.6. • Administer 2 mg/kg/d methylprednisolone or IV equivalents. • If corticosteroid refractory or no improvement after3 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.

11.2.11 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 26. 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 cause 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, 2018; Puzanov et al, 2017).

Table 26: 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 6.6 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 6.6 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 6.6. • 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.

11.2.12 Severe Cutaneous Adverse Reactions Management Algorithm

The following guidelines and Table 27 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 27: 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 necessarywith 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.

11.2.13 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 28. 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, 2018; 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 28: 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 6.6 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.

11.3 Appendix 3: RECIST Version 1.1

Tumor response will be assessed according to RECIST v1.1 (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 29.

Table 29: 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 30.

Table 30: 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 31.

Table 31: 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.

11.4 Appendix 4: iRECIST

The secondary assessment of tumor response will be according to a modified RECIST v1.1 for immune-based therapeutics, termed iRECIST (Seymour et al, 2017), as described below.

Responses assigned using iRECIST have a prefix of "i" (i.e., immune)—e.g., "immune" complete response (iCR), partial response (iPR), or stable disease (iSD), and unconfirmed progressive disease (iUPD) or confirmed progressive disease (iCPD)—to differentiate them from responses assigned using RECIST v1.1.

Table 32 presents a high-level comparison of RECIST v1.1 and iRECIST. The major change for iRECIST is the concept of resetting the bar if RECIST v1.1 progression is followed at the next assessment by tumor shrinkage. Other changes include assessment of new lesions, confirmation of progression, collection of reason why progression cannot be confirmed, and inclusion and recording of clinical status.

Table 32: Comparison of RECIST Version 1.1 and iRECIST

	RECIST Version 1.1	iRECIST
Definitions of measurable and nonmeasurable disease; numbers and site of target disease	Measurable lesions are ≥10 mm in diameter (≥15 mm for nodal lesions); maximum of 5 lesions (2 per organ); all other disease is considered non-target (must be ≥10 mm in short axis for nodal disease)	No change from RECIST v1.1; however, new lesions are assessed as per RECIST v1.1 but recorded separately on the case report form (but not included in the sum of lesions for target lesions identified at baseline)
CR, PR, or SD	Cannot have met criteria for progression before CR, PR, or SD	Can have had iUPD (1 or more instances), but not iCPD, before iCR, iPR, or iSD
Confirmation of CR or PR	Only required for non-randomized trials	As per RECIST v1.1
Confirmation of SD	Not required	As per RECIST v1.1
New lesions	Result in progression; recorded but not measured	Results in iUPD but iCPD are only assigned on the basis of this category if at next assessment additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions when none have previously been recorded can also confirm iCPD
Confirmation of progression	Not required (unless equivocal)	Required
Consideration of clinical status	Not included in assessment	Clinical stability is considered when deciding whether treatment is continued after iUPD

CPD=confirmed progressive disease; CR=complete response; iRECIST=immune Response Evaluation Criteria in Solid Tumors; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease; UPD=unconfirmed progressive disease. NOTE: "i" indicates immune responses assigned using iRECIST.

New Lesions

- New lesions should be assessed and categorized as measurable or non-measurable using RECIST v1.1 principles.
- Five lesions (no more than 2 per organ) should be measured and recorded as a new lesion target but should not be included in the sum of the measures of the original target lesions identified at baseline.
- Other new lesions (measurable/non-measurable) are recorded as new lesions non-target.
- New lesions do not need to meet the criteria for new lesion target to result in iUPD (or iCPD); new lesion non-target can also drive iUPD or iCPD.
- Progressive disease is confirmed (iCPD) in the new lesion category if the next imaging assessment (done at 4 to 8 weeks after iUPD) confirms additional new lesions or a further increase in new lesion size from iUPD (sum of measures increase in new lesion target ≥5 mm, any increase for new lesion non-target).

Timepoint Response

- In iRECIST there can be iSD, iPR, or iCR after RECIST v1.1 PD (Table 33 and Table 34).
  - 'Once a PD always a PD' is no longer the case.
  - First RECIST v1.1 PD is "unconfirmed" for iRECIST (termed iUPD).
  - iUPD must be confirmed at the next assessment (within 4-8 weeks).
  - If confirmed, termed iCPD.
- Timepoint response is based on:
  - Change from baseline (for iCR, iPR, iSD) or change from nadir (for PD).
  - The last i-response.

Progression

- Treatment past RECIST v1.1 PD should only be considered if the subject is clinically stable (recommendation – may be protocol-specific)
  - No worsening of performance status
  - No clinically relevant increase in disease-related symptoms
  - No requirement for intensified management of disease-related symptoms (analgesics, radiation, palliative care)
- Record the reason iUPD is not confirmed
  - Not stable
  - Treatment stopped but subject not reassessed/imaging not performed
  - iCPD never occurs

- Subject has died

- Confirmation of progression in iRECIST
  - Must be the NEXT assessment – if iSD, iPR, or iCR intervenes, then the bar is reset and iUPD must occur again and be confirmed (Figure 2).
  - Two ways to confirm:
    - Existing iUPD "gets worse"
    - Lesion category without iUPD previously now meets the (RECIST v1.1) criteria for PD
  - If confirmatory scans are not done, the reason must be documented.

Table 33: Assignment of Timepoint Response Using iRECIST

Lesions[a]			Timepoint Response With No Previous iUPD in Any Category	Timepoint Response with Previous iUPD in Any Category[b]
Target	Non-target	New		
iCR	iCR	No	iCR	iCR
iCR	Non-iCR/ non-iUPD	No	iPR	iPR
iPR	Non-iCR/ non-iUPD	No	iPR	iPR
iSD	Non-iCR/ non-iUPD	No	iSD	iSD
iUPD with no change, or with decrease from last timepoint	iUPD with no change, or decrease from last timepoint	Yes	Not applicable	New lesions confirm iCPD if new lesions were previously identified and they have increased in size (≥5 mm in sum of measures for new lesion target or any increase for new lesion non-target) or number; if no change is seen in new lesions (size or number) from last timepoint, assignment remains iUPD
iSD, iPR, iCR	iUPD	No	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in size of non-target disease (does not need to meet RECIST v1.1 for unequivocal progression)
iUPD	Non-iCR/ non-iUPD, or iCR	No	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in sum of measures ≥5 mm; otherwise, assignment remains iUPD

Lesions[a]			Timepoint Response With No Previous iUPD in Any Category	Timepoint Response with Previous iUPD in Any Category[b]
Target	Non-target	New		
iUPD	iUPD	No	iUPD	Remains iUPD unless iCPD is confirmed based on a further increase in previously identified target lesion iUPD in sum of measures ≥5 mm or non-target lesion iUPD (previous assessment need not have shown unequivocal progression)
iUPD	iUPD	Yes	iUPD	Remains iUPD unless iCPD confirmed on the basis of a further increase in previously identified target lesion iUPD in sum of measures ≥5 mm, previously identified non-target lesion iUPD (does no need to be unequivocal), or an increase in the size or number of new lesions previously identified
Non-iUPD or progression	Non-iUPD or progression	Yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of an increase in the size or number of new lesions previously identified

CPD=confirmed progressive disease; CR=complete response; iRECIST=immune Response Evaluation Criteria in Solid Tumors; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease; UPD=unconfirmed progressive disease

NOTE: "i" indicates immune responses assigned using iRECIST.

[a] Target lesions, non-target lesions, and new lesions defined according to RECIST v1.1 principles; if no pseudoprogression occurs, RECIST v1.1 and iRECIST categories for CR, PR, and SD would be the same.

[b] Previously identified in assessment immediately before this timepoint.

Table 34: Examples of Best Overall Response Assignments Using iRECIST

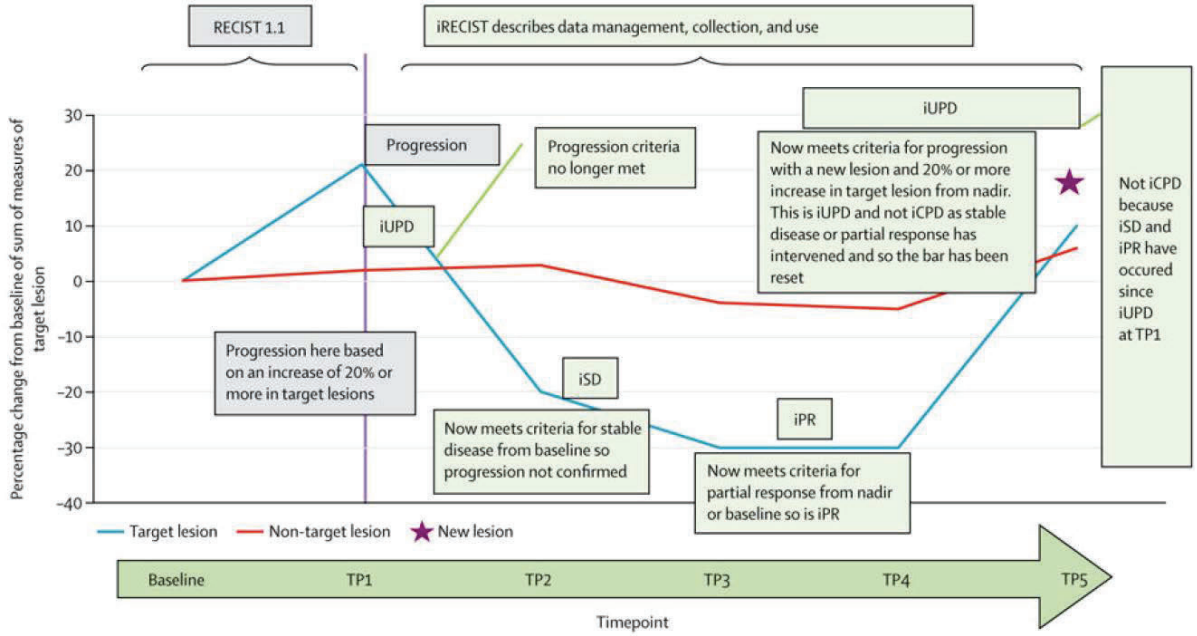
Example[a]	Timepoint Response 1	Timepoint Response 2	Timepoint Response 3	Timepoint Response 4	Timepoint Response 5	iBoR
1	iCR	iCR, iPR, iUPD, or NE	iCR, iPR, iUPD, or NE	iUPD	iCPD	iCR
2	iUPD	iPR, iSD, or NE	iCR	iCR, iUPD, or NE	iCR, iPR, iSD, iUPD, iCPD, or NE	iCR
3	iUPD	iPR	iPR, iSD, iUPD, or NE	iPR, iSD, iUPD, NE, or iCPD	iPR, iSD, iUPD, NE, or iCPD	iPR
4	iUPD	iSD or NE	iPR	iPR, iSD, iUPD, or NE	iPR, iSD, iUPD, iCPD, or NE	iPR
5	iUPD	iSD	iSD, iUPD, or NE	iSD, iUPD, iCPD, or NE	iSD, iUPD, iCPD, or NE	iSD
6	iUPD	iCPD	Any	Any	Any	iCPD
7	iUPD	iUPD (no iCPD)	iCPD	Any	Any	iCPD
8	iUPD	NE	NE	NE	NE	iUPD

CPD=confirmed progressive disease; CR=complete response; iRECIST=immune Response Evaluation Criteria in Solid Tumors; NE=not evaluable; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease; UPD=unconfirmed progressive disease

NOTE: "i" indicates immune responses assigned using iRECIST.

[a] Eight examples are presented for subjects with target disease at baseline, but many more scenarios exist following the same principles. Tables assume a randomized study in which confirmation of CR or PR is not required. For subjects with non-target disease only at baseline, only iCR and non-complete response or non-progression of disease can be assigned at each timepoint (not shown in the table for ease of presentation).

Figure 2: RECIST Version 1.1 and iRECIST: Example of Assessment



CPD=complete progressive disease; CR=complete response; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease; TP=timepoint; UPD=unconfirmed progressive disease.
Note: Prefix "i" indicates immune responses assigned using iRECIST; others without "i" are confirmed by RECIST v1.1.

11.5 Appendix 5: Response Criteria for Metastatic Castration-Resistant Prostate Cancer (Based on Prostate Cancer Clinical Trials Working Group 3 Criteria)

Prostate-specific Antigen (PSA)

As long as subject safety is the primary concern, in the absence of other indicators of disease progression, therapy should not be discontinued solely on the basis of a rise in PSA.

PSA progression is defined as the date that a 25% or greater increase and an absolute increase of 2 ng/mL or more from the nadir is documented and confirmed by a second value obtained 3 or more weeks later. Where no decline from baseline is documented, PSA progression is defined as a 25% increase from the baseline value along with an increase in absolute value of 2 ng/mL or more after 12 weeks of treatment.

Bone

Record post-treatment changes as either “no new lesions” or “new lesions.”

Progressing disease on bone scan is considered when at least 2 new lesions are observed. If these 2 or more new lesions are identified at the first post-treatment bone scans, progression remains unconfirmed unless at least 2 additional new lesions appear at a subsequent timepoint at least 6 or more weeks later (“2+2” rule). This is intended to account for bone scan flare response that is generally seen at earlier timepoints. If progression (defined as at least 2 new lesions on bone scan) is first identified at a timepoint beyond the first post-treatment bone scan (i.e., beyond the typical flare response window), then these 2 (or more) lesions should be confirmed on a subsequent bone scan, performed at least 6 weeks later. When further progression is documented on the confirmatory scan, the date of progression recorded for the trial is the date of the first scan that shows the change.

Table 35 shows the Prostate Cancer Clinical Trials Working Group outcomes measures.

Table 35: Prostate Cancer Clinical Trials Working Group Outcome Measures

Variable	Prevent/Delay Endpoints
PSA	**Decline from baseline:** record time from start of therapy to first PSA increase that is ≥25% and ≥2 ng/mL above the nadir that is confirmed by a second value 3 or more weeks later (i.e., a confirmed rising trend)[a] **No decline from baseline:** PSA progression ≥25% from baseline and ≥2 ng/mL increase from baseline after 12 weeks
Soft-tissue lesions	Use iRECIST criteria
Bone	The appearance of ~2 new lesions and, for the first reassessment only, a confirmatory scan performed 6 or more weeks later that shows at least 2 or more additional new lesions ("2+2" rule) If progression (2 or more new lesions) is identified at a timepoint beyond the first post-treatment scan, then these lesions must be confirmed on a subsequent scan. The date of progression is the date of the first scan that shows the change

iRECIST=immune-related Response Evaluation Criteria in Solid Tumors, PSA=prostate-specific antigen.

[a] Particularly important when anticipated effect on PSA is delayed or for biologic therapies.

Source: Scher et al, 2016

11.6 Appendix 6: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

11.6.1 Definitions

11.6.1.1 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

11.6.1.2 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: • 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) • Elective surgery planned prior to signing a consent • Admissions as per protocol for a planned medical/surgical procedure • Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy) • Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases. • 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.

11.6.1.3 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.

11.6.1.4 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.

11.6.2 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 11.6.1.2, 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)

11.6.3 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.

11.6.4 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 to the Sponsor will be via email with Safety Notification Forms and relevant documentation (SAE Form, Pregnancy Form, etc.).
- Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
- Reference Section 8.3.1 (time period and frequency for collecting AE, SAE, and other reportable safety event information) for reporting time requirements.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE, then the site can report this information on a paper SAE form or by telephone (see next section).
- Facsimile transmission or secure email of the SAE form is the preferred method to transmit this information to the Sponsor or designee.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting timeframes.
- Contacts for SAE and other reportable safety event reporting can be found in Section 8.3.8.2.

11.6.5 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 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 8.3.2.

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.

11.7 Appendix 7: Pregnancy Information

11.7.1 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.

11.7.2 Collection of Pregnancy Information

11.7.2.1 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.

11.7.2.2 Female Subjects who Become Pregnant

- 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 8.3.4. 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.

11.8 Appendix 8: Protocol Amendment History

Version Number	Section Number or Title	Description of Change	Reason for Change
4.0	Entire document	Minor spelling, grammar, punctuation, capitalization, and other formatting edits were made throughout the document	Consistency
4.0	Title, Section 2.1,	Title changed to add pembrolizumab as combination therapy to the title	To align with treatments in Cohort 10
4.0	Section 1.1	Synopsis updated to align with updates	To align with updates
4.0	Section 1.2	Figure 1 Study Schema: Updated to reflect changes in study design	To align with new cohorts and note discontinued cohorts
4.0	Section 1.3.1	Table 1 updated to: Include PD-L1 expression and CPS (testing required if historical results are not available or there has been intervening therapy)	To align with eligibility criteria of Cohort 10
4.0	Section 1.3.2	Text updated to include additional cohorts (Cohort 9 [28-day cycle] and Cohort 10 [21-day cycle]) and remove discontinued cohorts (Cohort 5 and Cohort 7 [21-day cycle])	To align with updated study design
4.0	Section 1.3.2	Table 2 updated to: • Include CXD8 assessments column • Include row and footnotes for gemcitabine and nab-paclitaxel administration on Days 1, 8, and 15 each 28-day cycle Add ECOG performance and pregnancy test assessments at C1D8	• To align with combination treatments administered in Cohort 9 • To align with combination treatments administered in Cohort 9 Safety monitoring
4.0	Section 1.3.2	Table 3 updated to: Include row and footnotes for pembrolizumab administration Q3W (Cohort 10)	To align with combination treatment administered in Cohort 10
4.0	Section 1.3.1, Section 1.3.2	Tables 1, 2, 3, and 6 updated to: • Include serum tumor markers CA 19-9 and CA 72-4	• To include additional serum tumor markers
4.0	Section 2.2.1.3	Section for renal cell carcinoma removed; renumbered section	Cohort removed
4.0	Section 2.2.1.5, Section 2.2.1.6	Sections for pancreatic adenocarcinoma and urothelial cell carcinoma added	To align with new cohorts (9 and 10)
4.0	Section 2.2.2.2	Updated clinical experience with TTX-030 from Study TTX-030-001 and Study TTX-030-002	To align with updated Investigator's Brochure

Version Number	Section Number or Title	Description of Change	Reason for Change
4.0	Section 2.2.3.1	Updated nonclinical experience to include 2-week GLP toxicity study results	To align with updated Investigator's Brochure
4.0	Section 2.2.3.2	Updated clinical experience with budigalimab	To align with updated Investigator's Brochure
4.0	Sections 2.2.8 – 2.2.11; Sections 2.3.5 – 2.3.6 Sections 4.3.5 - 4.3.6 Sections 6.6.2.5 – 6.6.2.6	New sections to provide background and rationale, risks and benefits, rationale for dose and schedule, and management of toxicities for treatments in new cohorts (gemcitabine + nab-paclitaxel in Cohort 9 and pembrolizumab in Cohort 10)	To align with new cohorts (9 and 10)
4.0	Section 3	Objectives changed to add pembrolizumab as combination therapy	
4.0	Section 4.1.1.2	Added the following statement: "Expansion to up to 40 subjects in select cohorts will be allowed based on review of safety, efficacy, and statistical considerations by the Sponsor and Cohort Review Committee, see Section 4.1.2 and Section 9.4. Subjects who are screened or enrolled into any of the discontinued cohorts below prior to cohort termination will continue on study as per protocol."	To allow for expansion in select cohorts and to describe continuation of subjects in discontinued cohorts.
4.0	Section 4.1.1.2	Added Cohort 9 (pancreatic adenocarcinoma) and Cohort 10 (urothelial cell carcinoma) Removed Cohort 5 and 7 Discontinued enrollment in Cohort 6	To align with updated study design
4.0	Section 4.2	Updated rationale for study design to include combination with gemcitabine/nab-paclitaxel (Cohort 9) and pembrolizumab (Cohort 10) and defined the TTX-030 RP2D in combination with budigalimab and mFOLFOX6.	To align with updated study design and report study results
4.0	Section 5.1	• Updated general inclusion criterion #7 to include caveat for ECOG score in Cohort 10 • Updated general inclusion criterion #8 to include "serum albumin ≥3.0 g/dL" • Removed Cohort 5 • Discontinued Cohort 6 and 7	To align with updated study design

Version Number	Section Number or Title	Description of Change	Reason for Change
		• Revised inclusion criteria for Cohort 8 Added inclusion criteria for Cohorts 9 and 10	
4.0	Section 6	Updated to include treatments in new cohorts (gemcitabine + nab-paclitaxel in Cohort 9 and pembrolizumab in Cohort 10)	To align with updated study design
4.0	Section 6.1	Table 6 Product Descriptions was updated, and Table 7 Study Treatments by Cohort was added to reflect the new cohorts and treatment regimens	To align with the updated study design
4.0	Section 7.1	Study drug discontinuation language updated to clarify that any other drugs cannot continue if TTX-030 is discontinued.	Clarity
4.0	Section 8.2.4	Updated to remove "±5 minutes" timepoint window for ECG.	Clarity
4.0	Section 9.1	Updated statistics section to update sample size to remove discontinued cohorts (5, 6, and 7) and to allow for expansion to up to 40 subjects in select cohorts	To align with updated study design.
4.0	Section 9.3.2	Efficacy analyses will be based on the Response Evaluable Population; the All Treated Population was removed for efficacy analyses.	Updated efficacy population
4.0	Section 9.4	Updated predictive probability based on interim data for 80% confidence and allowed for maximum sample size in Cohorts 4-10 from 23 to up to 40 at the discretion of the Sponsor and Cohort Review Committee	To align with updated study design
3.0	Entire document	Minor spelling, grammar, punctuation, capitalization, and other formatting edits were made throughout the document.	Consistency
3.0	Entire document	Tizona Therapeutics, Inc. to Trishula Therapeutics, Inc.	Company name change due to spin-out
3.0	Sponsor Approval Page	Update Medical Monitor	Personnel change
3.0	Section 1.3	Schedule of activities: - Clarify HPV status is only required if not known at screening - Update footnote for PK/PD draws collection - Extend archival biopsy collection requirement from 45 to 90 days	Clarity
3.0	Section 5.1	Inclusion Criteria:	

Version Number	Section Number or Title	Description of Change	Reason for Change
		- Update IC#3 to allow archival tumor tissue if collected within 90 days - Update IC#9 to reduce wash-out requirement from 28 to 14 days - Update IC#30 to allow mCRPC subjects who have had at least 1 prior second-generation anti-androgen therapy	- Recruitment flexibility - Treatment consideration for advanced/metastatic cancer population - Treatment consideration as standard of care is not required for mCRPC patients to receive both abiraterone and enzalutamid
3.0	Section 5.2	Inclusion Criteria: - Update EC#2 to reduce wash-out requirement from 28 to 14 days - Add EC#19 to exclude subjects with history of Stevens-Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN), or drug reaction with eosinophilia and systemic symptoms (DRESS). Add EC#25 to exclude subjects with hypersensitivity reactions to polysorbate 80	- Patient population and treatment consideration - Clarification of existing exclusion criteria for budigalimab potential risks - Safety consideration as budigalimab contains polysorbate 80
3.0	Section 6.5.1	Add pre-medication requirement for docetaxel	Safety monitoring
3.0	Section 8.3.8	Update Medical Monitor contact information	Change of Medical Monitor
3.0	Section 8.5	Update Table 11 Serum PK parameters	Clarity
3.0	Section 8.8	Extend archival biopsy collection requirement from 45 to 90 days	Clarity
3.0	Section 9.4	Update informal interim analysis plan for Cohorts 4, 5, 6, and 8	Clarity and enrollment consideration
3.0	Section 11.2.11	Update potential risks for budigalimab	Safety monitoring
2.0	Entire document	Minor spelling, grammar, punctuation, capitalization, and other formatting edits were made throughout the document	Consistency
2.0	Sections 1.1, 3.0	Primary and Secondary objectives	To include budigalimab in the analysis
2.0	Section 1.3	Schedule of Activities: -Added missing procedures due to errors -Added missing lab draws	Clarity and consistency
2.0	Section 5.0	-Removed inclusion criterion 3a(iii) -Updated inclusion criterion 8a	Clarity
2.0	Section 6.0	Added definitions for IMP and NIMP	Clarity

Version Number	Section Number or Title	Description of Change	Reason for Change
2.0	Section 7.1	-Removed specific under "Radiographic disease progression"	To align with schedule of activities
2.0	Section 8.0, 8.3.1	Added COVID-19 guidance	Safety monitoring
2.0	Section 8.2.4	Updated to only collect QTc interval data at minimum	To align with data collection objective
2.0	Section 8.7	Added "and/or clinical response"	To align with study objectives/endpoints

DOCUMENT HISTORY	
Document	**Date**
Version 1.0, Original Protocol	10 February 2020
Version 2.0, Amendment 1	06 July 2020
Version 3.0, Amendment 2 (Trishula)	22 October 2020
Version 4.0, Amendment 3 (Trishula)	06 April 2021
Version 5.0, Amendment 4 (Trishula)	09 September 2021

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