Protocol Title:	An Open-Label, Phase II, Randomized, Controlled Study of Danvatirsen Plus Pembrolizumab Compared to Pembrolizumab Alone in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (HNSCC)
Brief Title:	Activity and Safety of Danvatirsen and Pembrolizumab in HNSCC
Acronym:	PEMDA-HN
Protocol Number:	FLM-6774-201
Name of Investigational Product:	Danvatirsen
NCT Number:	05814666
Sponsor:	Flamingo Therapeutics Gaston Geenslaan 3, Building 4 3001 Leuven Belgium
Amendment 4 Document Date:	8 May 2025

CLINICAL STUDY PROTOCOL

Protocol Title:	An Open-Label, Phase II, Randomized, Controlled Study of Danvatirsen Plus Pembrolizumab Compared to Pembrolizumab Alone in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (HNSCC)
Short Protocol Title:	Activity and Safety of Danvatirsen and Pembrolizumab in HNSCC
Acronym:	PEMDA-HN
Protocol Number:	FLM-6774-201
Amendment:	4
Name of Investigational Product:	Danvatirsen
IND Number:	113825
IND Holder:	Flamingo Therapeutics
Sponsor:	Flamingo Therapeutics Gaston Geenslaan 3, Building 4 3001 Leuven Belgium
Original Protocol Date:	21 December 2022
Amendment 4 Date:	8 May 2025
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SPONSOR PROTOCOL APPROVAL SIGNATURE PAGE

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APPROVAL STATEMENT

The undersigned has reviewed the format and content of the above protocol and approved for issuance.

Approved by:

Signed by:
Andrew Denker
Signer Name: Andrew Denker
Signing Reason: I approve this document
Signing Time: 08-May-2025 | 9:59:09 PM CEST
697A2B118365432A9A1BBC035340DBD6

08-May-2025 | 9:59:25 PM CEST

Andrew Denker, MD; PhD
Chief Medical Officer

DATE

INVESTIGATOR ACCEPTANCE PAGE

I have read this protocol entitled:

An Open-Label, Phase II, Randomized, Controlled Study of Danvatirsen Plus Pembrolizumab Compared to Pembrolizumab Alone in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (HNSCC)

By signing below, the Investigator acknowledges that he/she has read and understands this protocol and will comply with the requirements for obtaining informed consent from all study participants prior to initiating any protocol-specific procedures, obtaining written initial and ongoing Institutional Review Board protocol review and approval, understands and abides by the requirements for maintenance of source documentation, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, trial specific manuals, Clinical Trial Agreement, ICH GCP guidelines, and all applicable national and local regulatory requirements.

Investigator Name (print)

Investigator Signature

Date

SYNOPSIS

Protocol Title	An Open-Label, Phase II, Randomized, Controlled Study of Danvatirsen Plus Pembrolizumab Compared to Pembrolizumab Alone in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (HNSCC)	
Study Phase	Phase II	
Objectives and Endpoints	*Primary Objective*	*Primary Endpoint*
	To determine the objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) as determined by the Investigator for the combination of danvatirsen and pembrolizumab compared with pembrolizumab alone as first-line treatment of patients with metastatic or unresectable, recurrent HNSCC whose tumors express programmed death-ligand 1 (PD-L1) by Combined Positive Score (CPS) ≥1	Confirmed ORR (partial response [PR] + complete response [CR] defined according to RECIST v1.1) (Eisenhauer et al 2009)
	Secondary Objectives	*Secondary Endpoints*
	To characterize the safety and tolerability of the combination of danvatirsen and pembrolizumab	Adverse events (AEs), serious adverse events, physical examinations, clinical laboratory values, and tolerability (dose interruptions/reductions)
	To evaluate additional efficacy parameters for the combination of danvatirsen and pembrolizumab compared with pembrolizumab alone	• Duration of response (DOR) by RECIST v1.1 • Disease control rate (DCR) and CR rate by RECIST v1.1 • ORR and DOR by RECIST v1.1 in tumors with CPS ≥20 and CPS ≥50 • Progression-free survival (PFS) by RECIST v1.1, defined as the time from randomization to the first documentation of progressive disease (PD) or death from any cause, whichever comes first • Overall survival (OS), defined as time from randomization to death from any cause
	To characterize the pharmacokinetics (PK) of danvatirsen	PK parameters derived from plasma concentrations of danvatirsen at

		defined timepoints in the combination regimen
	To determine the immunogenicity of danvatirsen	Anti-danvatirsen antibody titers at defined timepoints in the combination regimen
	Exploratory Objectives	*Exploratory Endpoints*
	• To determine the pharmacodynamic activity of danvatirsen in pre- and on-treatment tumor and blood specimens • To determine the relationship between clinical activity and human papillomavirus (HPV) and other biomarkers in pre- and on-treatment specimens	• STAT3 levels in pre- and on-treatment samples • Gene expression changes (RNA and/or protein) in pre- and on-treatment samples • Determination of HPV positivity
Study Design	Open-label, Phase II, randomized, controlled study evaluating the efficacy and safety of danvatirsen in combination with pembrolizumab compared with pembrolizumab alone as first-line treatment of patients with recurrent/metastatic (R/M) HNSCC. Two-thirds of patients will be randomized to receive danvatirsen and pembrolizumab and one-third will be randomized to receive pembrolizumab alone. Patients will be stratified by CPS (CPS ≥1 and <20 vs. CPS ≥20). An early assessment of response in patients with CPS ≥1 and <20 will be performed and should the response rate in this subgroup not pass the minimum desired efficacy level, eligibility will be restricted to patients with CPS ≥20.	
Study Visit Schedule and Procedures	The study consists of a screening period, treatment period, safety follow-up, and survival follow-up. After the screening period (Day -28 to Day -1), eligible patients will be randomized in a 2:1 ratio to receive either danvatirsen + pembrolizumab or pembrolizumab monotherapy, respectively. The treatment period consists of sequential 21-day treatment cycles. Patients will receive study treatment until PD, unacceptable toxicity, or voluntary withdrawal. Patients with an initial assessment of PD may remain on treatment until a confirmatory scan is performed at least 4 weeks later to confirm PD prior to removing the patient from study treatment, as long as the progression does not represent a safety risk in the Investigator's judgment. Patients who discontinue study treatment for any reason will have a safety follow-up visit 30 days (+7 days) after the last dose of study treatment and a follow-up for AEs 90 days (+7 days) after the last dose of pembrolizumab. Survival information, including survival status and initiation of new anticancer treatment(s), will be collected every 12 weeks (±7 days) during the survival follow-up period. The patients may be contacted remotely, and the information collected will be recorded in an electronic case report form.	
Number of Sites	Approximately 35 sites globally	

Number of Patients	Approximately 81 patients
Study Population	To be eligible to participate in this study, candidates with R/M HNSCC must meet all of the following eligibility criteria within 28 days of Cycle 1 Day 1 or at the timepoint specified in the individual eligibility criterion. **Inclusion Criteria** 1. Must have given written informed consent (signed and dated). 2. Patient is ≥18 years old or age of majority in the country in which they reside, whichever is higher. 3. Recurrent/metastatic histologically or cytologically proven squamous cell carcinoma of the head and neck that is considered incurable by local therapy. Eligible primary tumor locations are oropharynx, oral cavity, hypopharynx, and larynx. 4. Presence of measurable tumor per RECIST v1.1 criteria. 5. Detectable PD-L1 expression in tumor, defined as CPS ≥1 determined by a test approved by US FDA or national regulatory agency of the country in which the patient resides. • A Tumor Proportion Score (TPS) value ≥30 may be used for initial eligibility however a CPS value must be obtained and reported utilizing a tissue sample obtained prior to the start of study treatment. Examples of approved tests include PD-L1 IHC 22C3 pharmDx (Dako North America, Inc.); PD-L1 IHC 28-8 pharmDx (Dako North America, Inc.); Ventana PD-L1 (SP142) Assay (Ventana Medical Systems, Inc.); Ventana PD-LI (SP263) Assay (Ventana Medical Systems, Inc) 6. Baseline fresh tumor biopsy or archival specimen. A fresh biopsy is preferred if safe and feasible to obtain and consented to by the patient (details provided in section on **Tissue Samples**). 7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. 8. Adequate organ function within 10 days of study treatment, including the following: • Absolute neutrophil count ≥1,500/μL • Platelet count ≥100,000/μL • Hemoglobin ≥9 g/dL (may be with transfusion) • Serum creatinine within normal limits or for patients with serum creatinine above institutional normal: – Creatinine clearance ≥45 mL/min – Creatine clearance can be calculated using an appropriate standard formula (e.g. Modification of Diet in Renal Disease equation [MDRD], Cockcroft-Gault formula or another formula that is typically used at the institution), or can be obtained from a 24-hour urine collection. • Total bilirubin ≤1.5× upper limit of normal (ULN) • Aspartate aminotransferase (serum glutamic oxaloacetic transaminase) and alanine aminotransferase (serum glutamic pyruvic transaminase)

	≤2.5× ULN in the absence of liver metastases or ≤5× ULN in the presence of liver metastases • International normalized ratio or prothrombin time (PT) and activated partial thromboplastin time or partial thromboplastin time (PTT) ≤1.5× ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants 9. Oxygen saturation on room air ≥92% by pulse oximetry. 10. Patients must satisfy the following criteria: • Females: must be non-pregnant and non-lactating and either: i. Surgically sterile (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy) ii. Postmenopausal (defined as 12 months of spontaneous amenorrhea in females >55 years of age or, in females ≤55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and follicle-stimulating hormone levels in the postmenopausal range for the laboratory involved) iii. Abstinent* or iv. If engaged in sexual relations and of childbearing potential, agree to use highly effective contraceptive methods (Appendix 3) from the time of signing the informed consent form (ICF) until at least 4 months after the last dose of study treatment • Males, if engaged in sexual relations with a female of childbearing potential, must use an acceptable method of birth control (i.e. condom in line with the Clinical Trials Facilitation Group guidance) from the time of signing the ICF until at least 4 months after the last dose of study treatment. *Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a study, and withdrawal are not acceptable methods of contraception. 11. Has an estimated life expectancy of at least 3 months. 12. Has recovered from all complications or surgery and all toxicities of prior therapy to ≤Grade 1 (or baseline) by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE v5.0) (exceptions: peripheral neuropathy ≤Grade 2 and any toxicities that in the view of the Investigator are not a clinically significant safety risk for further therapy administration, such as but not limited to: alopecia, fatigue, erectile dysfunction, hot flashes, cough, and urinary incontinence). **Exclusion Criteria** 1. Prior therapy for metastatic HNSCC. Systemic therapy for locoregionally recurrent HNSCC that was completed more than 3 months prior to signing consent is allowed if given as part of multimodal treatment for locally advanced disease. 2. Has disease suitable for local therapy with curative intent. 3. Primary tumor of the nasopharynx.

	4. Has received prior therapy with an anti-programmed death 1 (PD-1), anti-PD-L1, or anti-programmed death-ligand-2 (PD-L2). 5. Radiation therapy (or other non-systemic therapy) within 2 weeks of Day 1 of study treatment. 6. Known autoimmune disease that has required systemic treatment (i.e., use of disease modifying agents, corticosteroids, or immunosuppressive drugs) in the past year. Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroids for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. 7. Known immunodeficiency or receiving systemic steroid therapy that would be the equivalent of >10 mg prednisone daily or any other form of immunosuppressive therapy within 7 days prior to Day 1 of study treatment. • Patients with known immunodeficiency conditions in which the number of immune cells is not impacted may be enrolled. 8. Prior allogeneic tissue/solid organ transplant. 9. Has any of the following cardiac criteria: a. Any abnormalities in rhythm, conduction, or morphology of resting 12-lead electrocardiogram (ECG) that in the opinion of the Investigator render the patient unsuitable for participation in the study b. Mean resting corrected QT interval (QTc) calculated using Fridericia's formula >450 msec for males and >470 msec for females according to local assessment and obtained from 3 ECGs performed approximately 2 minutes apart (exception: patients stable on pacemaker with higher QTc) c. Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalemia, congenital long QT syndrome, any concomitant medication known to prolong the QT interval, or family history of long QT syndrome or unexplained sudden death under 40 years of age 10. Has received a live vaccine within 30 days of planned start of study treatment. 11. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Day 1 of study treatment. 12. History of (non-infectious) pneumonitis that required steroids or current pneumonitis. 13. History of other malignancies, except the following: a. Malignancy treated with curative intent and with no known active disease present for ≥3 years before the first dose of study treatment and felt to be at low risk for recurrence by treating physician. b. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease. c. Adequately treated carcinoma in situ without evidence of disease. 14. Pregnant or breastfeeding; a negative pregnancy test is required within 14 days of randomization for all women of childbearing potential. 15. Active infection with human immunodeficiency virus (HIV) except patients who are currently stable on antiretroviral therapy (ART) for at least 4 weeks and agree to adhere to ART during study treatment, have HIV viral load of <400 copies per milliliter at screening (or undetectable per local criteria), and have cluster of differentiation 4 (CD4) T-cell counts ≥200/μL.

	16. Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. For patients with evidence of HBV infection, the HBV viral load must be undetectable on suppressive therapy, if indicated. For patients with HCV, infection must have been treated and cured or patients must be currently on treatment and have an undetectable HCV viral load. 17. Treated or untreated parenchymal brain metastases or leptomeningeal disease. Current active malignant epidural disease is also excluded. Previously treated epidural disease does not exclude the patient from study as long as disease is inactive. (Note: Computed tomography or magnetic resonance imaging of brain is not needed to rule these out unless the patient has clinical symptoms suggestive of central nervous system metastases.) 18. Treatment with another investigational drug, biological agent, or device within 1 month of screening, or 5 half-lives of investigational agent (if known), whichever is longer. 19. As judged by the Investigator, any evidence of severe or uncontrolled systemic disease (e.g., unstable or uncompensated respiratory, cardiac, hepatic, or renal disease or impairment), laboratory finding or history of substance abuse or psychiatric disorder that makes it undesirable for the patient to participate in the study and/or comply with study procedures. 20. Hypersensitivity to any component of danvatirsen or pembrolizumab.
Study Drug Dosage and Administration	Treatment cycles are based on the schedule of administration of pembrolizumab. Each cycle is considered 21 days in length. The maximum duration of treatment with pembrolizumab is 24 months. There will be no limit on the duration of treatment with danvatirsen. <u>Danvatirsen dosing</u> Week 1: Danvatirsen 3 mg/kg intravenously (IV) on Days 1, 3, and 5 (±1 day) over 1 hour (±10 minutes) Week 2 and subsequent weeks: Danvatirsen 3 mg/kg IV weekly (±2 days) over 1 hour (±10 minutes) <u>Pembrolizumab dosing</u> Pembrolizumab 200 mg IV every 3 weeks (±7 days) over 30 minutes (-5 min/+10 min) Infusion of danvatirsen should be completed at least 60 minutes (Cycle 1) or at least 30 minutes (in subsequent cycles if no infusion reaction in first cycle) before the start of the pembrolizumab infusion on days that both drugs are administered.
Adjustment of Dose and/or Treatment Schedule	See section on **Dose Modification Guidelines and Toxicity Management** for specific toxicities.
Safety Plan	Safety and toxicity will be continuously monitored in the study under the guidance from the Safety Review Committee. In addition, the committee will evaluate the safety data from the first 9 patients randomized who have completed at least one cycle of study treatment for any unexpected toxicities, discontinuations due to study drug-related toxicities, or other signals that may raise safety concerns. Accrual to the study will be suspended if this analysis is

	not completed by the time the 20th patient is randomized to the study. If the combination is deemed intolerable, further accrual will be halted.
Statistical Considerations	**Sample Size** Sample size considerations were based on monitoring the primary efficacy endpoint, ORR, using a 2-arm Bayesian optimal phase 2 (BOP2) design. The primary efficacy evaluation will be the magnitude of ORR in each of the treatment arms and the probability that the combination arm ORR is superior to that of the control (monotherapy) arm, that is $Pr(ORR_{comb} > ORR_{con} \mid data)$. The design is optimized to maximize the power under H_0:$ORR_{con} = 0.15$ and $ORR_{comb} = 0.43$, while controlling the type I error rate at 1-sided 0.05. An interim futility analysis is planned when ORR can be assessed for the first 39 patients, and the final ORR analysis is planned after 81 patients are followed for a minimum of 3 months (2 radiologic scans). A 2:1 combination:control randomization will be used for the 2 arms and will yield 83% power at the 1-sided 5% alpha based on the decision rule to reject the null hypothesis and conclude that the combination arm is superior compared to the control. **Analysis Populations** • Full Analysis Set (FAS): All patients who receive at least 1 dose of study treatment based on the treatment assigned at randomization; this will be the primary analysis set for efficacy analyses. • Safety Analysis Set: All patients who receive at least 1 dose of study treatment based on the actual treatment received; this will be the primary analysis set for safety analyses. • PK Evaluable Set: All FAS patients with evaluable PK data. • Biomarker Evaluable Set: All FAS patients with evaluable biomarker data. **Safety Analysis** The analysis of safety will focus on AEs with summaries of treatment-emergent adverse events (TEAEs, i.e., AEs that start or increase in severity after the first dose of study treatment). AEs will be coded according to the latest Medical Dictionary for Regulatory Activities (MedDRA) version available at the time of database creation. The severity of AEs will be graded according to NCI CTCAE v5.0. Safety summaries will also be provided for laboratory tests, vital signs, ECOG performance status, ECG, and weight parameters. **Efficacy Analysis** The primary efficacy analysis for ORR, as well as the interim analysis for PFS and OS, will be conducted once all patients are treated and followed for a minimum of 3 months (2 radiologic scans). The final analysis for PFS and OS will be conducted after all patients have been followed for a minimum of 15 months, unless the study is deemed futile at the interim or primary analysis stage. ORR and DCR will be reported along with the corresponding 2-sided 90% and 95% Clopper-Pearson exact confidence interval, and a comparison between the 2 treatment groups will be performed based on Fisher's exact test.

	DOR, PFS, and OS will be summarized using Kaplan-Meier methods. PFS and OS comparisons between the 2 groups will be performed using the stratified log rank test. **Interim Analyses** Safety Analysis The Safety Review Committee will meet regularly to monitor the safety of the combination regimen throughout this study. Cumulative safety data from the first 9 patients randomized who have completed at least one cycle of study treatment will be reviewed. Accrual to the study will be suspended if this analysis is not completed by the time the 20th patient is randomized to the study. Futility Analysis The BOP2 suggested futility monitoring criteria for the entire study population, as well as the CPS ≥1 and <20 subgroup, are non-binding. At the primary analysis, a lower ORR for advancement may also suffice by taking into consideration the CR rate that suggests superiority with regard to deep responses over that observed with pembrolizumab alone.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
16mer ASO	16-nucleotide antisense oligonucleotide
ACC	American College of Cardiology
ACTH	adrenocorticotropic hormone
ADA	anti-drug antibody
ADEM	acute disseminated encephalomyelitis
ADL(s)	activity(ies) of daily living
AE	adverse event
AHA	American Heart Association
AI	adrenal insufficiency
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ART	antiretroviral therapy
ASCO	American Society of Clinical Oncology
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
ATG	antithymocyte globulin
AUC_{tau}	area under the plasma concentration-time curve over the dosing interval
BAL	bronchoalveolar lavage
BOP2	Bayesian optimal phase 2
BOR	best overall response
BSA	body surface area
BU	Bethesda units
BUN	blood urea nitrogen
C	cycle
c/w	coupled with
CAD	coronary artery disease
CD4	cluster of differentiation 4
CD52	cluster of differentiation 52
cEt	constrained ethyl
CFR	Code of Federal Regulations

Abbreviation	Definition
CHEST	American College of Chest Physicians
CI	confidence interval
CIADM	checkpoint inhibitor–associated autoimmune diabetes
CK	creatine kinase
C_{max}	maximum concentration recorded
CMV	cytomegalovirus
CNS	central nervous system
CPS	Combined Positive Score
CRI	chronic renal insufficiency
CRO	contract research organization
CSF	cerebrospinal fluid
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough concentration
CXR	chest X-ray
CYP	cytochrome P450
D	day
DCR	disease control rate
DI	diabetes insipidus
DIHS	drug-induced hypersensitivity syndrome
DKA	diabetic ketoacidosis
DLCO	diffusing capacity of lung for carbon monoxide
DMARD	disease-modifying anti-rheumatic drug
DOR	duration of response
DRESS	drug reaction with eosinophilia and systemic symptoms
DVT	deep vein thrombosis
EBV	Epstein-Barr virus
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ED	emergency department

Abbreviation	Definition
EDC	electronic data capture
EGD	esophagogastroduodenoscopy
EMG	electromyography
EOT	end of treatment
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEIBA	factor eight inhibitor bypassing activity
FFPE	formalin-fixed paraffin-embedded
FT4	free thyroxine
GBS	Guillain-Barre syndrome
GCP	Good Clinical Practice
GI	gastrointestinal
Gx	grade, where x is a number
HBV	hepatitis B virus
HCV	hepatitis C virus
Hgb	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HNSCC	head and neck squamous cell carcinoma
HPV	human papillomavirus
HUS	hemolytic-uremic syndrome
ICF	informed consent form
ICH	International Council for Harmonisation
ICU	intensive care unit
IEC	Independent Ethics Committees
IgG	immunoglobulin G
IL-6	interleukin-6
INR	international normalized ratio
irAE	immune-related adverse event
IRB	Institutional Review Board
IRR	infusion-related reaction
IRT	Interactive Response Technology

Abbreviation	Definition
ITP	idiopathic thrombocytopenic purpura
IV	intravenous(ly)
IVIG	intravenous immunoglobulin
LDH	lactate dehydrogenase
LLN	lower limit of normal
LMWH	low-molecular-weight heparin
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MGFA	Myasthenia Gravis Foundation of America
MMF	mycophenolate mofetil
MRI	magnetic resonance imaging
mRNA	messenger RNA
NA	not applicable
NASH	nonalcoholic steatohepatitis
NCI	National Cancer Institute
NMO	neuromyelitis optica
NSAID	non-steroidal anti-inflammatory drug
ON	optic neuritis
ORR	objective response rate
OS	overall survival
PB	peripheral blood
PBMC	peripheral blood mononuclear cell
PCP	primary care practitioner
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed death 1
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PEX	plasma exchange
PFS	progression-free survival
PK	pharmacokinetic
PMN	polymorphonuclear cell
PR	partial response

Abbreviation	Definition
PT	prothrombin time
PTT	partial thromboplastin time
QTc	corrected QT interval
QW	weekly
QxW	every x weeks
R/M	recurrent/metastatic
RBC	red blood cell
RECIST v1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
ROW	Rest of World
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Safety Analysis Set
SCAR	severe cutaneous adverse reaction
SJS	Stevens-Johnson syndrome
SoA	Schedule of Activities
SSKI	potassium iodide
SUSAR	suspected unexpected serious adverse reaction
T2DM	Type 2 diabetes mellitus
TEAE	treatment-emergent adverse event
TEN	toxic epidermal necrolysis
T_{max}	time to maximum plasma concentration
TNFα	tumor necrosis factor alpha
TPS	Tumor Proportion Score
TSH	thyroid-stimulating hormone
TTP	thrombotic thrombocytopenic purpura
ULN	upper limit of normal
US	United States
UTI	urinary tract infection
VKA	vitamin K antagonist
WBC	white blood cell

1 INTRODUCTION

1.1 Background

1.1.1 Head and Neck Cancer

Head and neck cancer is the sixth most common cancer worldwide, with the predominant histology being head and neck squamous cell carcinoma (HNSCC) (Sung et al 2020). In the United States (US), HNSCC accounts for 3% of all cancers diagnosed annually and 2% of cancer-related deaths. The majority of patients with HNSCC initially present with locally advanced disease. Despite aggressive, combined modality treatment, a significant proportion of patients will develop recurrent or metastatic (R/M) disease that is no longer amenable to curative therapy. Existing treatment options include platinum-based doublets, epidermal growth factor receptor inhibition, and immunotherapy. However, outcomes are generally poor, and most patients die within a year of diagnosis of R/M HNSCC (NCCN 2022). Targeted immunotherapy promoting anti-tumor T-cell activity initially demonstrated improved survival and durable objective responses in many different cancers (Galon and Bruni 2019). As programmed death-ligand 1 (PD-L1) expression is observed in close to 68% of patients with HNSCC regardless of human papillomavirus (HPV) status, targeting programmed death 1 (PD-1)/PD-L1 in HNSCC was a rational approach for study (NCCN 2022). Initially, pembrolizumab was studied in a Phase Ib study in patients with R/M disease and demonstrated an objective response rate (ORR) of 18%, and later the benefit was confirmed in the second-line setting (Ferris et al 2016). The benefit was comparable between HPV-positive and HPV-negative groups.

Pembrolizumab is also approved for use in R/M disease. Indeed, the data from the KEYNOTE-048 study reshaped the current standard of care in the frontline R/M HNSCC setting (Burtness et al 2019). Both single-agent pembrolizumab and pembrolizumab in combination with chemotherapy were evaluated against the existing standard-of-care regimen in this setting. Single-agent pembrolizumab demonstrated a 19% ORR (5% complete response [CR]) and 23% ORR (8% CR) in the subsets of Combined Positive Score (CPS) ≥1 and CPS ≥20 populations, respectively. There was also improvement on overall survival (OS) but not in progression-free survival (PFS). The totality of the data led to the approval of Keytruda® (pembrolizumab) in combination with platinum and fluorouracil for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC and as a single agent for the first-line treatment of patients whose tumors express PD-L1 (CPS ≥1) as determined by a Food and Drug Administration (FDA)-approved test.

1.1.2 Danvatirsen

Danvatirsen (AZD9150, ISIS 481464) is a 16-nucleotide antisense oligonucleotide (16mer ASO) designed to target and down-regulate expression of human STAT3 messenger RNA (mRNA). It is a phosphorothioate-modified chimeric antisense oligonucleotide (ASO) with a 10-base central oligonucleotide core that supports mediated metabolism, flanked by 3 constrained ethyl (cEt)-modified nucleosides on both the 5′ and 3′ ends (Seth et al 2009). The novel cEt chemical modification incorporated into danvatirsen is anticipated, based on extensive preclinical studies, to confer properties similar to second generation 2′ methoxyethyl chemical modifications, but with a potential for enhanced potency.

The target of danvatirsen, STAT3, is generally regarded as undruggable by more traditional approaches. STAT3 belongs to the STAT family of transcription factors and is a promising cancer drug target because of its pleiotropic involvement in tumorigenesis. STAT3 regulates the expression of many genes directly important to the survival of tumor cells (Alvarez et al 2005). In addition, it plays an important role in non-tumor cells of the tumor microenvironment involved in immune evasion of tumor cells, angiogenesis, and metastasis (Kortylewski et al 2009).

Preclinical studies of danvatirsen administered intravenously (IV) led to a rapid initial clearance from plasma, followed by a much slower elimination phase due to extensive tissue distribution (most notably in the kidneys). Anti-drug antibodies (ADAs) were detected in the plasma of some animals.

In vitro cytochrome P450 (CYP) drug interaction studies demonstrated that danvatirsen drug-drug interaction is not expected to be a risk through inhibition of CYP activity, particularly at clinically appropriate concentrations. However, this potential effect cannot be completely excluded.

Preclinical toxicity studies showed that danvatirsen is generally well tolerated. Proinflammatory effects were noted in several organs, including liver, along with minor elevations in liver function tests. Overall, the toxicology findings were similar to those noted with similar ASOs.

To date, well over 500 patients with hematologic malignancies or solid tumors have been exposed to danvatirsen, and several doses, schedules, and infusion times have been evaluated. Both monotherapy and combination therapy with other anticancer agents have been studied. Consistent with the preclinical data, a bi-phasic pharmacokinetic (PK) profile was noted with an initial fast distribution phase (half-life of 2 to 3 hours) followed by a slower elimination phase. With regard to adverse events (AEs), risks included thrombocytopenia, liver enzyme elevations, anemia, and neutropenia. Overall, danvatirsen demonstrated a tolerable safety profile, and toxicities were well managed with standard guidelines.

The most relevant study of danvatirsen with regard to HNSCC is the SCORES study, which evaluated the addition of danvatirsen to checkpoint blockade. This study included both first-line and second-line patients with R/M HNSCC. The ORR was assessed in 66 evaluable patients treated with danvatirsen at a dose of 3 mg/kg weekly in combination with durvalumab in the first-line setting. In this patient population that was not selected for PD-L1 expression, ORR was 23% (CR 9.1%). The duration of response (DOR) was 42 weeks, indicating a clinically meaningful benefit. Considering that danvatirsen monotherapy in this anti-PD-L1 naïve HNSCC patient population showed no responses, and the historical ORR with durvalumab as monotherapy is also generally regarded as negligible, the combination of danvatirsen and durvalumab appeared to be active and well tolerated. Moreover, additional analyses showed an intriguing relationship between PD-L1 levels and ORR and CRs. In patients with CPS ≥1 or CPS ≥20, the combination of danvatirsen and durvalumab led to an ORR of 31% to 37%, and 33% to 43%, respectively (note that the range is due to lack of CPS measures in some patients) and to a CR rate of 11% to 13% in the CPS≥1 subgroup and 19% to 22% in the CPS ≥20 subgroup. These outcomes are numerically superior to pembrolizumab historical data in this population.

For the most up-to-date clinical information regarding danvatirsen, refer to the latest version of the Investigator's Brochure.

1.1.3 Pembrolizumab

Binding of the PD-1 ligands, PD-L1 and programmed death-ligand 2 (PD-L2), to the PD-1 receptor found on T cells inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors, and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth. Other checkpoint inhibitors, including the PD-1 inhibitor nivolumab and the PD-L1 inhibitor durvalumab, have also been studied in head and neck cancer. Pembrolizumab and nivolumab have shown activity in large studies and have been FDA approved for use in R/M HNSCC.

For the most up-to-date clinical information regarding pembrolizumab, refer to the latest version of the KEYTRUDA product insert.

1.2 Rationale for Study Design and Dose Regimen

The SCORES study combined danvatirsen and durvalumab in different cohorts of patients with R/M HNSCC. The dose and schedule of administration of danvatirsen that will be used in this study are derived primarily from the SCORES study where they were shown to be safe and effective in a similar patient population when combined with a full dose of durvalumab. However, SCORES used a 1-week run-in period in which patients were treated with danvatirsen alone 3 times weekly for 1 week as a loading strategy prior to the addition of durvalumab for the combination phase. As the standard of care has evolved and pembrolizumab is now approved, the dosing and loading strategy for danvatirsen has been modified such that both danvatirsen and pembrolizumab dosing commence on the first day of the first cycle. The two additional doses of danvatirsen in the first week of dosing are likely to be tolerable in view of the relatively short circulation time of danvatirsen. The longer tissue half-life of danvatirsen is expected to take more time and ultimately be comparable to the steady-state phase of dosing with both drugs after 1 or more weeks.

The dose and schedule of administration of pembrolizumab chosen for this study are already approved for the frontline treatment of HNSCC and are described further in the KEYTRUDA product insert. Two schedules of administration for pembrolizumab are currently approved in the HNSCC setting: every 3 weeks (Q3W) and every 6 weeks. Among those two schedules, the Q3W schedule has been chosen as it was the schedule used in the KEYNOTE-048 study.

The benchmark efficacy data for this study are derived primarily from KEYNOTE-048 and informed by the data from the SCORES study. This study is designed to test the hypothesis that the data from the SCORES study evaluating the combination of danvatirsen and an anti-PD-L1, durvalumab, can be replicated with an anti-PD-1, pembrolizumab, in HNSCC. This is an important objective as durvalumab has not achieved approval while pembrolizumab is approved in frontline HNSCC and has been widely adopted as the standard of care in appropriate patients. The study will enroll patients with a CPS ≥1 because these patients are hypothesized to derive greater benefit from the combination of danvatirsen and

pembrolizumab. Stratification will occur based on CPS to determine if higher PD-L1 expression predicts a higher response rate. Finally, the randomized design is chosen to rigorously assess the anticipated improvement of the dual regimen of danvatirsen and pembrolizumab versus pembrolizumab alone. The primary endpoint of ORR will be assessed by the Investigator. It is anticipated that this design will yield robust efficacy data to inform additional studies that may be pivotal in intent.

1.3 Benefits and Risks

This study is intended to generate new information about the efficacy and safety of the investigational agent danvatirsen when combined with pembrolizumab, which is approved for frontline R/M HNSCC. Patients who choose to participate generally cannot expect to receive direct additional benefit from the combination regimen than that provided by pembrolizumab alone. However, based on the preceding SCORES study, which evaluated danvatirsen in combination with durvalumab, an antibody that is mechanistically similar to pembrolizumab, the benefit:risk profile of this novel combination should be favorable and allow for a detailed and thorough characterization of the efficacy and safety of the combination regimen in a biomarker-selected patient population that is likely to derive greater benefit than the patient population that was included in SCORES. Nevertheless, the tolerability of the experimental combination regimen is currently unknown. Every attempt will be made to scrutinize the qualitative and quantitative nature of drug-related toxicities continuously and at a formal analysis early in the course of the study to ensure that the safety of the combination is acceptable.

2 STUDY OBJECTIVES AND ENDPOINTS

Objectives and Endpoints	
Objective	***Endpoint***
Primary	
To determine the ORR by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) as determined by the Investigator for the combination of danvatirsen and pembrolizumab compared with pembrolizumab alone as first-line treatment of patients with metastatic or unresectable, recurrent HNSCC whose tumors express PD-L1 by CPS ≥1	Confirmed ORR (partial response [PR] + CR defined according to RECIST v1.1) (Eisenhauer et al 2009)
Secondary	
To characterize the safety and tolerability of the combination of danvatirsen and pembrolizumab	AEs, serious adverse events (SAEs), physical examinations, clinical laboratory values, and tolerability (dose interruptions/reductions)
To evaluate additional efficacy parameters for the combination of danvatirsen and pembrolizumab compared with pembrolizumab alone	• DOR by RECIST v1.1 • Disease control rate (DCR) and CR rate by RECIST v1.1 • ORR and DOR by RECIST v1.1 in tumors with CPS ≥20 and ≥50 • PFS by RECIST v1.1, defined as the time from randomization to the first documentation of progressive disease (PD) or death from any cause, whichever comes first • OS, defined as time from randomization to death from any cause
To characterize the PK of danvatirsen	PK parameters derived from plasma concentrations of danvatirsen at defined timepoints in the combination regimen
To determine the immunogenicity of danvatirsen	Anti-danvatirsen antibody titers at defined timepoints in the combination regimen
Exploratory	
• To determine the pharmacodynamic activity of danvatirsen in pre- and on-treatment tumor and blood specimens • To determine the relationship between clinical activity and HPV and other	• STAT3 levels in pre- and on-treatment samples • Gene expression changes (RNA and/or protein) in pre- and on-treatment samples • Determination of HPV positivity

biomarkers in pre- and on-treatment specimens	

3 STUDY DESIGN

3.1 Overall Study Design

This is a multicenter, open-label, Phase II, randomized, controlled study to determine the efficacy, safety, and other indicators of clinical and biological activity of the combination of danvatirsen and pembrolizumab as first-line treatment for R/M HNSCC.

After providing informed consent, patients will be assessed for eligibility during the screening phase of the study. All patients must be willing and able to provide a formalin-fixed paraffin-embedded (FFPE) archival or fresh tumor sample collected during the screening period; a fresh biopsy is preferred if safe and feasible to obtain and consented to by the patient. Following the screening period, eligible patients will be randomized in a 2:1 ratio to danvatirsen + pembrolizumab or pembrolizumab monotherapy, respectively.

Patients will be stratified by CPS (CPS ≥1 and <20 vs. CPS ≥20). An early assessment of response in patients with CPS ≥1 and <20 will be performed and should the response rate in this subgroup not pass the minimum desired efficacy level, eligibility will be restricted to patients with CPS ≥20.

Patients will receive treatment in 21-day cycles. Patients assigned to the pembrolizumab monotherapy arm will receive treatment until a criterion for discontinuation is met or a maximum of 24 months/34 cycles of treatment. Patients assigned to combination therapy will receive both treatments until a criterion for discontinuation is met or the patient has received a maximum of 24 months/34 cycles of pembrolizumab, after which they may remain on danvatirsen monotherapy.

As the combination of danvatirsen and pembrolizumab has not been evaluated previously, safety will be assessed on a continuous basis. A formal review of safety will be performed by the Safety Review Committee after the first 9 patients randomized have completed at least one cycle of the assigned study treatment. If accrual reaches 20 patients prior to availability of the safety results, accrual will be suspended. If the combination is deemed intolerable, further accrual will be halted.

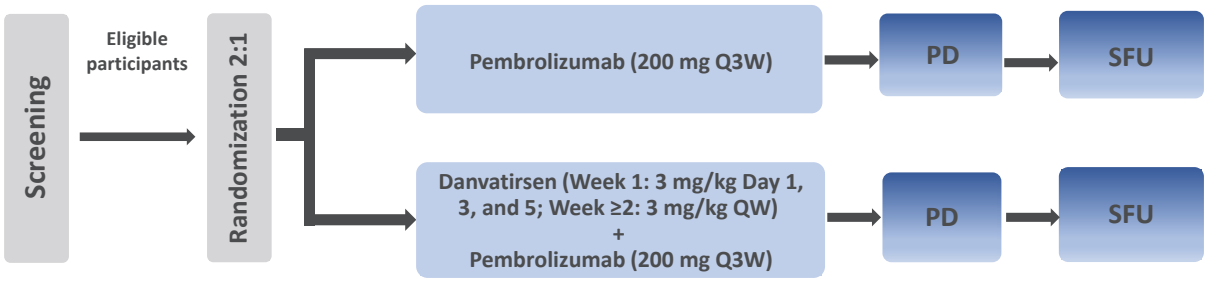
A futility analysis will be conducted when ORR can be assessed for the first 39 patients, as described in more detail in Section 9.2.

Patients in both treatment arms will have radiologic tumor assessments every 6 weeks (±1 week), regardless of treatment delays, until objective disease progression, initiation of new anticancer treatment, death, withdrawal of consent, or end of study, whichever occurs first.

All patients who discontinue study treatment for any reason will have a safety follow-up visit 30 days (+7 days) after the last dose of study treatment and a follow-up for AEs 90 days (+7 days) after the last dose of pembrolizumab. Patients will be followed for survival at 12-week (±7 days) intervals until death or withdrawal of consent, whichever occurs first. Survival follow-up will continue until at least 15 months after the last patient is randomized in the study.

The study design is depicted in Figure 1.

Figure 1: Study Scheme



Note: Maximum duration of pembrolizumab treatment is 24 months; there is no limit to the duration of danvatirsen treatment.
Abbreviations: PD = progressive disease; Q3W = every 3 weeks; QW = weekly; SFU = safety follow-up & survival follow-up

3.2 Definition of End of Study

A patient is considered to have completed the study upon completion of the last scheduled procedure shown in the Schedule of Activities (SoA) (Section 8.1), including the survival follow-up.

End of study is defined as the date of the last visit of the last patient.

3.3 Duration of Study Participation

Study participation includes the screening, treatment, and follow-up periods. The screening period is 28 days. After randomization, patients receive treatment in 21-day cycles. The maximum duration of treatment with pembrolizumab is 24 months; there will be no limit of the duration of treatment with danvatirsen.

The follow-up period includes safety follow-up until 30 days (+7 days) after the last dose of study treatment, follow-up for AEs until 90 days (+7 days) after the last dose of pembrolizumab, and survival follow-up every 12 weeks (±7 days) until death or withdrawal of consent, whichever occurs first. Survival follow-up will continue until at least 15 months after the last patient is randomized in the study.

3.4 Randomization and Blinding

Randomization will be managed centrally through an Interactive Response Technology (IRT) system. Patients will be randomized in a 2:1 ratio to either danvatirsen + pembrolizumab or pembrolizumab monotherapy. Randomization will be stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 vs. 1 [Appendix 1]) for patients enrolled under the original protocol or Amendment 1.

For patients enrolled following this amendment, randomization will be stratified by the CPS (CPS ≥1 and <20 vs. CPS ≥20) obtained during screening, instead of ECOG performance status. Considering the addition of the new subgroup of subjects (CPS ≥1 and <20) as of this amendment, the change in stratification variables will not impact the intended randomization balance. Removing ECOG performance status as a potential second stratification variable in addition to CPS is necessary considering the limited size of the study and the 2:1 randomization ratio.

Sites will receive the randomized treatment assignment for all patients by logging into the IRT system and entering the required data.

Patients who are randomized in the IRT but do not receive study treatment will not be replaced.

Blinding is not applicable for this open-label study.

4 STUDY POPULATION

To be eligible to participate in the study, candidates with R/M HNSCC must meet all of the eligibility criteria within 28 days of Cycle 1 Day 1 or at the timepoint specified in the individual eligibility criterion.

4.1 Inclusion Criteria

To be eligible for study participation, all of the following inclusion criteria must be met:

1. Must have given written informed consent (signed and dated).
2. Patient is ≥18 years old or age of majority in the country in which they reside, whichever is higher.
3. Recurrent/metastatic histologically or cytologically proven squamous cell carcinoma of the head and neck that is considered incurable by local therapy. Eligible primary tumor locations are oropharynx, oral cavity, hypopharynx, and larynx.
4. Presence of measurable tumor per RECIST v1.1 criteria.
5. Detectable PD-L1 expression in tumor, defined as CPS ≥1 determined by a test approved by US FDA or national regulatory agency of the country in which the patient resides. A TPS value ≥30 may be used for initial eligibility however a CPS value must be obtained and reported utilizing a tissue sample obtained prior to the start of study treatment.
   - Examples of approved tests include PD-L1 IHC 22C3 pharmDx (Dako North America, Inc.); PD-L1 IHC 28-8 pharmDx (Dako North America, Inc.); Ventana PD-L1 (SP142) Assay (Ventana Medical Systems, Inc.); Ventana PD-LI (SP263) Assay (Ventana Medical Systems, Inc)
6. Baseline fresh tumor biopsy or archival specimen. A fresh biopsy is preferred if safe and feasible to obtain and consented to by the patient (details provided in section on **Tissue Samples** [Section 7.12.1]).
7. ECOG performance status of 0 or 1.
8. Adequate organ function within 10 days of study treatment, including the following:
   a. Absolute neutrophil count ≥1,500/µL
   b. Platelet count ≥100,000/µL
   c. Hemoglobin ≥9 g/dL (may be with transfusion)
   d. Serum creatinine within normal limits or, for patients with serum creatinine above institutional normal:
      - Creatinine clearance ≥45 mL/min
      - Creatine clearance can be calculated using an appropriate standard formula (e.g. Modification of Diet in Renal Disease equation [MDRD], Cockcroft-Gault formula, or another formula that is typically used at the

institution) or can be obtained from a 24-hour urine collection.(Appendix 2)

e. Total bilirubin ≤1.5× upper limit of normal (ULN)

f. Aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase) and alanine aminotransferase (ALT) (serum glutamic pyruvic transaminase) ≤2.5× ULN in the absence of liver metastases or ≤5× ULN in the presence of liver metastases

g. International normalized ratio (INR) or prothrombin time (PT) and activated partial thromboplastin time or partial thromboplastin time (PTT) ≤1.5× ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

9. Oxygen saturation on room air ≥92% by pulse oximetry.
10. Patients must satisfy the following criteria:
    a. Females: must be non-pregnant and non-lactating and either:
        i. Surgically sterile (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy)
        ii. Postmenopausal (defined as 12 months of spontaneous amenorrhea in females >55 years of age or, in females ≤55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and follicle-stimulating hormone levels in the postmenopausal range for the laboratory involved)
        iii. Abstinent* or
        iv. If engaged in sexual relations and of childbearing potential, agree to use highly effective contraceptive methods (Appendix 3) from the time of signing the informed consent form (ICF) until at least 4 months after the last dose of study treatment
    b. Males, if engaged in sexual relations with a female of childbearing potential, must use an acceptable method of birth control (i.e. condom in line with the Clinical Trials Facilitation Group guidance) from the time of signing the ICF until at least 4 months after the last dose of study treatment.

* Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a study, and withdrawal are not acceptable methods of contraception.

11. Has an estimated life expectancy of at least 3 months.
12. Has recovered from all complications or surgery and all toxicities of prior therapy to ≤Grade 1 (or baseline) by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE v5.0) (exceptions: peripheral neuropathy ≤Grade 2 and any toxicities that in the view of the Investigator are not a clinically significant safety risk for further therapy administration, such as but not

limited to: alopecia, fatigue, erectile dysfunction, hot flashes, cough, and urinary incontinence).

4.2 Exclusion Criteria

A patient will be ineligible for study participation if any of the following exclusion criteria are met:

1. Prior therapy for metastatic HNSCC.
   Systemic therapy for locoregionally recurrent HNSCC that was completed more than 3 months prior to signing consent is allowed if given as part of multimodal treatment for locally advanced disease.
2. Has disease suitable for local therapy with curative intent.
3. Primary tumor of the nasopharynx.
4. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2.
5. Radiation therapy (or other non-systemic therapy) within 2 weeks of Day 1 of study treatment.
6. Known autoimmune disease that has required systemic treatment (i.e., use of disease modifying agents, corticosteroids, or immunosuppressive drugs) in the past year. Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroids for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
7. Known immunodeficiency or receiving systemic steroid therapy that would be the equivalent of >10 mg prednisone daily or any other form of immunosuppressive therapy within 7 days prior to Day 1 of study treatment.
   - Patients with known immunodeficiency conditions in which the number of immune cells is not impacted may be enrolled.
8. Prior allogeneic tissue/solid organ transplant.
9. Has any of the following cardiac criteria:
   a. Any abnormalities in rhythm, conduction, or morphology of resting 12-lead electrocardiogram (ECG) that in the opinion of the Investigator render the patient unsuitable for participation in the study
   b. Mean resting corrected QT interval (QTc) calculated using Fridericia's formula >450 msec for males and >470 msec for females according to local assessment and obtained from 3 ECGs performed approximately 2 minutes apart (exception: patients stable on pacemaker with higher QTc)
   c. Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalemia, congenital long QT syndrome, any concomitant medication known to prolong the QT interval, or family history of long QT syndrome or unexplained sudden death under 40 years of age
10. Has received a live vaccine within 30 days of planned start of study treatment.

11. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Day 1 of study treatment.
12. History of (non-infectious) pneumonitis that required steroids or current pneumonitis.
13. History of other malignancies, except the following:
    a. Malignancy treated with curative intent and with no known active disease present for ≥3 years before the first dose of study treatment and felt to be at low risk for recurrence by treating physician.
    b. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
    c. Adequately treated carcinoma in situ without evidence of disease.
14. Pregnant or breastfeeding; a negative pregnancy test is required within 14 days of randomization for all women of childbearing potential.
15. Active infection with human immunodeficiency virus (HIV) except patients who are currently stable on antiretroviral therapy (ART) for at least 4 weeks and agree to adhere to ART during study treatment, have HIV viral load of <400 copies per milliliter at screening (or undetectable per local criteria), and have cluster of differentiation 4 (CD4) T-cell counts ≥200/µL.
16. Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. For patients with evidence of HBV infection, the HBV viral load must be undetectable on suppressive therapy, if indicated. For patients with HCV, infection must have been treated and cured or patients must be currently on treatment and have an undetectable HCV viral load.
17. Treated or untreated parenchymal brain metastases or leptomeningeal disease. Current active malignant epidural disease is also excluded. Previously treated epidural disease does not exclude the patient from study as long as disease is inactive. (Note: Computed tomography [CT] or magnetic resonance imaging (MRI) of brain is not needed to rule these out unless the patient has clinical symptoms suggestive of central nervous system metastases).
18. Treatment with another investigational drug, biological agent, or device within 1 month of screening, or 5 half-lives of investigational agent (if known), whichever is longer.
19. As judged by the Investigator, any evidence of severe or uncontrolled systemic disease (e.g., unstable or uncompensated respiratory, cardiac, hepatic, or renal disease or impairment), laboratory finding or history of substance abuse or psychiatric disorder that makes it undesirable for the patient to participate in the study and/or comply with study procedures.
20. Hypersensitivity to any component of danvatirsen or pembrolizumab.

5 STUDY TREATMENTS AND CONCOMITANT THERAPY

5.1 Study Treatments

Danvatirsen is the investigational medicinal product (IMP). Pembrolizumab is the standard of care. Collectively, these 2 drugs are referred to as the "study treatments" in this protocol. Information on dose and schedule of administration is provided in Table 1.

Table 1: Doses and Schedule of Administration

Study Treatment Name	Danvatirsen	Pembrolizumab
Unit dose strength	Danvatirsen 50 mg/mL	Pembrolizumab 25 mg/mL
Dosage level	3 mg/kg	200 mg fixed dose
Dose formulation	Concentrate for solution for infusion	Concentrate for solution for infusion
Route of administration	IV infusion	IV infusion
IMP	IMP	Standard of care
Sourcing	Sponsor	Study center
Packaging and labeling	IMP will be provided in glass vials. Each vial will be labeled per FDA requirements.	Commercial package

Abbreviations: FDA = Food and Drug Administration; IMP = investigational medicinal product; IV = intravenous

Danvatirsen will be administered via an IV infusion at 3 mg/kg on Days 1, 3, and 5 of Cycle 1 Week 1 with a ±1 day dosing window and ensuring there is at least 1 day between each danvatirsen dose, i.e. danvatirsen should not be dosed on consecutive days. Note: The visit windows on D1, D3 and D5 do not apply to patients that are participating in the intense PK subset. Danvatirsen is dosed weekly thereafter beginning on Days 8 and 15 of Cycle 1 and on Days 1, 8, and 15 of each subsequent 3-week cycle. Starting at Cycle 1 Week 2, danvatirsen has a ±2-day dosing window.

Pembrolizumab will be administered via an IV infusion on Day 1 of each 3-week treatment cycle after all procedures and assessments have been completed. Pembrolizumab has a ±7-day dosing window.

On days when both danvatirsen and pembrolizumab are administered, danvatirsen will be administered first. After a window of at least 60 minutes, pembrolizumab will be administered. In the absence of Grade 2 or greater hypersensitivity reactions, the window of time between the two infusions may be reduced to 30 minutes after the first cycle.

Danvatirsen may be held to allow for recovery of toxicities (See Section 5.4.2 for further guidance on dose modifications). Doses missed during the hold will be considered skipped, and the patient should receive their next dose at the scheduled time.

Pembrolizumab may be delayed to allow for recovery of toxicities (See Section 5.4.3 for further guidance on dose modifications). Doses missed during the hold will be considered skipped, and the patient should receive their next dose at the scheduled time.

5.2 Preparation, Storage, Handling, and Accountability

5.2.1 Danvatirsen

Danvatirsen will be administered as a dose of 3 mg/kg over 1 hour (±10 minutes, the infusion may be extended beyond the 10 minute window as medically indicated). The patient's weight within 14 days of Cycle 1 Day 1 dosing should be used to calculate the dose. The dose is not recalculated if the patient's weight changes during the study.

Danvatirsen vials are to be stored at the study center in a secured facility with limited access and controlled temperature following the labeled storage conditions. The temperature should be monitored on a daily basis and documented on the temperature monitoring log or equivalent. Should a temperature excursion occur, the vials should be quarantined in a secure, temperature controlled (2°C to 8°C/36°F to 46°F) area and the Sponsor notified.

In accordance with International Council for Harmonisation (ICH) and local regulatory requirements, the Investigator and/or the person responsible for dispensing study treatment must be able to account for all study treatment provided to the site and patient at all times.

The IMP must be dispensed only at the study site, and no study medication is to be used outside of this study. At the conclusion of the study, all used and unused study medication shipped to the Investigator should be destroyed on site after reconciliation procedures with the study monitor are complete. A destruction certificate will be required.

Further guidance and information on preparation, handling, storage, accountability, and final disposition of unused danvatirsen are provided in the Pharmacy Manual.

5.2.2 Pembrolizumab

Pembrolizumab vials should not be used beyond the expiration date provided by the manufacturer.

Pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes [-5 min/+10 min]). The infusion time may be extended beyond the 10min window if medically indicated.

Pembrolizumab should be stored according to the package insert.

Refer to the package insert for further instructions.

5.2.3 General Study Drug Administration

Do not co-administer other drugs through the same IV line.

Do not administer as an IV push or bolus.

5.3 Study Treatment Compliance

Study treatment will be administered IV at the study center. The administration of study treatment will be documented in the appropriate section of the electronic case report form (eCRF).

5.4 Dose Modification Guidelines and Toxicity Management

5.4.1 Purpose and Approach

If a patient experiences a clinically significant and/or unacceptable toxicity with the study treatment, dosing will be interrupted or the dose reduced. Supportive therapy will be administered as required.

If the toxicity resolves or improves to at least Grade 1 or pretreatment baseline (refer to specific toxicity criteria in Section 5.4.2 for danvatirsen and Section 5.4.3 for pembrolizumab) by day 21 for danvatirsen and day 42 for pembrolizumab, dosing may resume.

If the toxicity does not resolve (refer to specific toxicity criteria in Section 5.4.2 for danvatirsen and Section 5.4.3 for pembrolizumab) or at least improve after 21 days for danvatirsen or 42 days for pembrolizumab, dosing may still be resumed after discussion and agreement with the medical monitor.

Dose modification should only be applied if the toxicity is **at least possibly related** to study treatment and in the absence of alternative etiologies.

- When more than one toxicity is noted simultaneously with different grades of severity, the **highest grade** should be used to guide dose modification decisions.
- As one arm of this study is a combination regimen and some side effects of danvatirsen and pembrolizumab can be overlapping (e.g., possible ALT/AST elevations, thrombocytopenia, and neutropenia), every effort should be made to **attribute the toxicity to the component part** of the study treatment regimen, and **only the dose of the component part should be modified**. If the Investigator has any questions with regard to such an AE, the Investigator should immediately contact the Medical Monitor.
- In the absence of clear alternative etiology, all events of an inflammatory nature should be considered immune related.
- The reasons for dose modifications, actions taken, and outcomes will be recorded.
- For concomitant medications, dose modifications will be at the discretion of the Investigator in accordance with the severity of the toxicity.
- For temporary delays in study treatment due to toxicity, the **cycle structure** should **remain** and not be regarded as delayed. Following the resolution of toxicity, the treatment regimen will resume as previously scheduled. This plan will potentially result in skipped doses and is intended to keep the treatment cycles synchronized with study assessments.

5.4.2 Dose Modifications for Danvatirsen

One dose reduction of danvatirsen will be allowed for an individual patient, to 2 mg/kg weekly. Dose reductions are required for elevations in liver function tests and are also permitted, at Investigator's discretion, for other toxicities/AEs after they have resolved to grade 1 or pretreatment baseline, following discussion with the medical monitor and approval. If the dose reduction is not tolerated, study treatment should be permanently discontinued, and the patient should be followed up for safety. Once the dose of danvatirsen is reduced, it cannot be re-escalated.

If danvatirsen is held at Day 1 of a cycle, pembrolizumab should be continued and danvatirsen resumed at the next opportunity (i.e., according to the cycle schedule).

Dose modifications for elevations in liver function tests are shown in Table 2, and dose modifications for all other AEs are shown in Table 3.

Table 2: Dose Modifications for Elevations in Liver Function Tests

Severity of Event	Dose Adjustment for Danvatirsen
Grade 1	No change.
Grade 2	No change.
Grade 3	1st occurrence: Hold administration of danvatirsen until the AE recovers to Grade 0-1 or to pretreatment baseline AE level, then re-start at the lower dose upon resolution. 2nd occurrence: Discontinue.
Grade 4	Discontinue.

Abbreviation: AE = adverse event

Table 3: Dose Holds for All Other Adverse Events

Severity of Event	Dose Adjustment for Danvatirsen
Grade 1	Maintain danvatirsen dose level and provide treatment to control symptoms, if applicable.
Grade 2 (tolerable)	Maintain danvatirsen dose level and provide treatment to control symptoms, if applicable.
Grade 2 (intolerable or recurrent)	Hold administration of danvatirsen until the AE recovers to Grade 0-1 or to pretreatment baseline AE level, whichever is more abnormal. Then, resume treatment.
Grade 3	Hold administration of danvatirsen until the AE recovers to Grade 0-1 or to pretreatment baseline AE level, whichever is more abnormal. Then re-start at the same dose or lower dose at the discretion of the Investigator and approval by the medical monitor
Grade 4	Discontinue.

Abbreviation: AE = adverse event

5.4.3 Dose Holds for Pembrolizumab

Dose delays are allowed for pembrolizumab; dose reductions are not allowed.

American Society of Clinical Oncology (ASCO) guidelines for the workup and management of immune-related toxicities should be followed (Schneider et al 2021 https://ascopubs.org/doi/pdf/10.1200/JCO.21.01440).

Appendix 4 presents a summary of those guidelines adapted for pembrolizumab for a rapid reference but is not a substitute for the complete guidelines.

5.4.4 Management of Other Toxicities

All other hematologic and non-hematologic toxicities should be managed according to standard medical practice and should adhere to commonly accepted guidelines. For example, while the prophylactic use of colony-stimulating factors is not allowed during the first administration of study treatment for any patient, for subsequent administrations, ASCO guidelines should be followed for the therapeutic use of granulocyte colony-stimulating factor in patients with Grade 3-4 febrile neutropenia in addition to appropriate workup for sepsis, antibiotics and/or other anti-infectives, and other supportive care.

Patients should also receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

5.5 Concomitant Medications

A concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins and supplements. Every effort should be made to optimize the well-being of a patient through appropriate supportive care. All prior and concomitant medications taken from 30 days prior to enrollment in the study until 30 days after the patient's last dose of study treatment must be recorded on the eCRF.

5.5.1 Hematopoietic Growth Factors

Primary prophylactic use of granulocyte colony-stimulating factors is not permitted during Cycle 1 of treatment, but they may be used to treat treatment-emergent neutropenia as indicated by the current ASCO guidelines.

In subsequent cycles, the use of hematopoietic growth factors is at the discretion of the treating physician in line with local guidelines. Patients who enter the study on stable doses of erythropoietin or darbepoietin may continue this treatment, and patients may start either drug during the study at the discretion of the treating physician.

5.5.2 Concomitant Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and administration of IMPs to minimize the risk

of impaired wound healing and bleeding has not been determined. In case of a surgical procedure, IMPs should be delayed. Postoperatively, the decision to reinitiate IMPs should be discussed with the Sponsor.

5.5.3 Concomitant Radiotherapy

Palliative radiotherapy is not permitted during study treatment.

5.5.4 Supportive Care

- Nausea/Vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake.
- Anti-infectives: Patients with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating Investigator for a given infectious condition, according to standard institutional practice.
- Anti-inflammatory or narcotic analgesics may be offered as needed.
- Patients who need to be on anticoagulant therapy during treatment should be treated with low molecular weight heparin. If low molecular weight heparin cannot be administered, coumadin or other coumarin derivatives or other anti-coagulants (including direct Factor Xa inhibitors) may be allowed; however, appropriate monitoring of PT/INR should be performed.

5.6 Prohibited Medications

The concomitant use of the following therapies is prohibited while on study except as noted below:

- Immunosuppressive agents, unless used to treat drug-related AEs.
- Immunosuppressive doses of systemic corticosteroids.
  - Steroid use at prednisone dose (or dose equivalent) ≤10 mg/day is allowed but must be kept to a minimum.
  - Corticosteroids as premedication for allergic reactions (e.g., IV contrast) or as a management of AEs are allowed.
- Any live, attenuated vaccine within 30 days prior to Day 1 of study treatment or at any time during the study. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed. Note: Authorized COVID-19 vaccines are allowed.
- Any concurrent anti-neoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy other than study treatment, palliative radiation therapy, or standard or investigational anticancer agents).

5.6.1 Precautionary Medications

Drugs that are metabolized by CYP should be used with caution.

6 DISCONTINUATION AND WITHDRAWAL CRITERIA

6.1 Discontinuation of Study Treatment

After consultation with the medical monitor, patients in the combination arm that are discontinued from one of the study treatments may remain in the study and continue to receive the other study treatment until a discontinuation criterion for the remaining treatment has been met.

Treatment with danvatirsen and pembrolizumab should be permanently discontinued for any of the following:

- Consent withdrawal
- Intolerable AE or an AE that meets the criteria for discontinuation
- Confirmed PD
    - Clinically stable patients who experience radiographic PD by RECIST v1.1 may continue to receive study treatment if patients are otherwise tolerating study treatment in the opinion of the Investigator and there are no signs of rapid, radiographic progression of disease or progression at critical anatomical sites (e.g., cord compression or tumor impinging on a major blood vessel) requiring urgent alternative interventions. Confirmatory imaging should be performed at least 4 weeks later for patients with PD who remain on study treatment. If PD is confirmed, the patient will withdraw from study treatment.
- Clinical progression, in absence of radiographic progression by RECIST v1.1, including intolerable signs or symptoms consistent with disease progression, rapidly worsening laboratory values or relevant tumor markers, rapid decline in ECOG performance status, or impingement of the tumor at critical anatomic sites requiring urgent interventions. Whenever possible, discontinuation due to clinical progression should be discussed with the Medical Monitor
- Pregnancy
- Significant patient non-compliance with the protocol or major protocol deviation
- Investigator decision
- Sponsor decision to end the study.

Patients who discontinue study treatment will complete end-of-treatment (EOT) procedures, safety follow-up, and will enter the survival follow-up phase, as specified in the SoA (Section 8.1). See Section 7.6 for more information.

6.2 Patient Withdrawal from the Study

Any patient may voluntarily withdraw consent at any time and for any reason. In addition, the Investigator may withdraw a patient due to clinical and compliance considerations, and the Sponsor may withdraw a patient due to safety, administrative, or compliance reasons.

Withdrawal may be from the study treatment phase only or from the entire study, including the requisite follow-up visits.

If such withdrawal occurs, or if the patient fails to return for visits, the Investigator must determine the primary reason for a patient's withdrawal from the study and record the information on the eCRF. If the reason for withdrawal is an AE, monitoring should continue until the outcome is evident. The specific event or test result(s) must be recorded in the eCRF.

It should be clearly documented in the source data whether patients withdrew their consent from all study procedures and will not enter the follow-up phase, or if the patient withdrew their consent for study treatment and procedures but will continue participation in the follow-up phase.

If a patient withdraws consent for the survival follow-up phase, the study site is still obligated to follow the patient's survival status through publicly available forms of information (i.e., death registries) .

The Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

6.3 Lost to Follow-up

A patient will be considered lost to follow-up if they repeatedly fail to return for scheduled visits, and the study site is unable to make contact. Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient. These contact attempts (e.g., 3 phone calls followed by a certified letter) should be documented in the patient's medical record. Should the patient continue to be unreachable, they will be considered to have withdrawn from the study.

If a patient is lost to follow-up, the study site is still obligated to follow the patient's survival status through publicly available forms of information (i.e., death registries).

7 STUDY ASSESSMENTS AND PROCEDURES

Study assessments and procedures are described in the SoA (Section 8.1).

The Investigator and Sponsor will conduct the study in accordance with ICH Good Clinical Practice (GCP) and local regulations. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct, and the Investigator must ensure that study procedures are performed as described in the protocol. During the study, procedures and observations will be monitored to confirm that study requirements are being followed as outlined in the SoA.

7.1 Informed Consent Form

Informed consent may be obtained any time prior to screening procedures, no visit window applies. ICFs for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

The anticipated consents to be used in the study are listed below; however, individual Institutional Review Boards (IRBs)/Ethics Committees (ECs) may require additional consent.

1. General Informed Consent: Consents patients for all required study procedures.
2. Optional Tissue Study Informed Consent (US patients only): Consented patients who are able and willing to provide fresh tumor tissue at C2D1, and EOT. As noted in the eligibility criteria, a fresh biopsy at screening is also preferred if safe and feasible to obtain and consented to by the patient.

7.2 Screening

All screening procedures must be performed within 28 days prior to the first treatment (Cycle 1 Day 1), unless otherwise stated in the SoA (Section 8.1). Procedures conducted as part of the patient's routine clinical management (e.g., blood count) and obtained before signing the ICF may be used for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.

All inclusion and exclusion criteria will be reviewed by the Investigator or qualified designee to ensure that the patient qualifies for the study. Eligibility will also be reviewed by the Sponsor or designee. In the event of borderline laboratory results or other factors that are deemed clinically insignificant, procedures may be repeated to meet eligibility requirements fully and/or discussed with the Medical Monitor for potential inclusion.

Demographic data, baseline characteristics, and medical and surgical history will be obtained during screening.

History of the cancer under study will be recorded separately. This will include, but is not limited to, data on histopathological diagnosis, grading, staging, sites of metastases, prior treatments, prior best response, and diagnostic and biomarker data.

7.3 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently assigned to study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria not met, and any SAEs related to study procedures that occur after the ICF was signed.

Individuals who do not meet the criteria for participation in the study may rescreen by repeating the individual assessment(s) for which they failed.

7.4 Prior, Concomitant, and Post-Treatment Medication Reviews

Prior medications: Prior medications taken by the patient within 30 days of enrollment into the study and all ongoing medications will be recorded. Prior treatments for the current cancer will be recorded separately and not listed among prior medications.

Concomitant medications: Medications taken by the patient during the study will be recorded from the date of consent through the 30-day safety follow-up.

Concomitant cancer-related procedures: Cancer-related procedures during the study will be recorded from the date of consent through the 30-day safety follow-up.

Post-treatment anticancer therapy: The Investigator or qualified designee will review all new anticancer therapy initiated after the last dose of study treatment. If a patient initiates a new anticancer therapy within 4 weeks after the last dose of study treatment, the 30-day safety follow-up visit must occur before the first dose of the new therapy. Once new anticancer therapy has been initiated, patients will move into survival follow-up.

7.5 Treatment Period

Patients should continue to receive study treatments and assessments as defined in the SoA (Section 8.1) until treatment discontinuation criteria are met (Section 6.1).

7.6 End-of-Treatment Visits

EOT visit requirements are described in the SoA (Section 8.1).

The EOT visit should occur as soon as possible at the time both study treatments are discontinued. If the EOT visit occurs approximately 30 days from the last dose of study treatment, the procedures performed at the EOT visit can serve as the 30-day safety follow-up and do not need to be repeated.

7.6.1 30-Day Safety Follow-up

The 30-day safety follow-up visit is required for all patients 30 days (+7 days) after the last dose of study treatment or before initiation of new anticancer treatment, whichever comes first. Patients with an AE of Grade ≥2 will be further followed until the resolution of the AE

to Grade 0-1 or until initiation of new anticancer therapy, whichever occurs first. Patients with an ongoing treatment-related AE must be followed until it resolves, becomes stable, or is considered not clinically significant by the Investigator.

7.6.2 90-Day Safety Follow-up

All patients who discontinue pembrolizumab will be contacted (telephone communication or clinic visit, at the Investigator's discretion) for the follow-up of AEs 90 days (+7 days) after the last dose of pembrolizumab or before initiation of new anticancer treatment, whichever comes first.

7.6.3 Survival Follow-up

All patients who have discontinued the study treatment will continue to be followed for survival information, including survival status and initiation of new anticancer treatment(s). Survival information will be collected every 12 weeks (±7 days) (telephone communication or in clinic visit) until the study ends. Survival data will be obtained from public records for patients who have been lost to follow-up.

Patients who discontinue study treatment for reasons other than PD will continue to have tumor assessments performed every 6 weeks until PD or the initiation of new anticancer therapy.

7.7 Imaging Assessments

For all patients, tumor response assessment will be obtained by radiographic imaging with contrast-enhanced CT (preferred) or MRI evaluation. Optimal anatomic coverage for most solid tumors include the chest, abdomen, and pelvis. Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. In general, lesions present at baseline should be followed using the same imaging methodology and imaging equipment at subsequent assessments.

Tumor response assessments will be based on evaluation of response of target, non-target, and new lesions according to RECIST v1.1, as detailed in Appendix 5 (all measurements should be recorded in metric notation). Following initial objective response (PR or CR per RECIST v1.1), confirmatory imaging studies should be obtained 4 to 6 weeks later (Eisenhauer et al 2009).

Before stopping treatment, confirmation of PD should be considered by imaging no less than 4 weeks after initial progression.

The timing of on-study imaging should follow calendar days and **should not** be adjusted for delays in treatment administration or for visits. The same imaging technique should be used in a patient throughout the study for consistency.

For patients who discontinue study treatment for reasons other than PD, radiographic scans should continue according to the respective schedule of assessment until PD, initiation of new anticancer therapy, withdrawal of consent, or at least 15 months after the last patient is

randomized in the study, whichever comes first. Additional imaging may be performed if clinically indicated per the Investigator's discretion.

Brain MRI with or without contrast is the preferred brain imaging modality; however, CT is acceptable if MRI is clinically contraindicated. Patients with treated or untreated parenchymal brain metastases, leptomeningeal disease, or current active malignant epidural disease are excluded from participation in the study (see Section 4.2). Patients with previously treated epidural disease are allowed as long as disease is inactive. Patients are not required to have brain imaging at screening unless there are suggestive clinical symptoms/suspicion.

During the study, brain CT/MRI scans should be conducted if clinically indicated by development of new specific symptoms.

7.8 Safety Assessments

7.8.1 Physical Examination

The Investigator or qualified designee will perform a complete physical examination during the screening period, on Day 1 of each cycle, and at the end of the treatment period as specified in the SoA (Section 8.1). Clinically significant abnormal findings during screening should be captured in the medical history.

Patients on the danvatirsen and pembrolizumab arm will have a targeted physical examination as directed by disease, signs, and symptoms performed on Days 8 and 15 of each cycle and at the 30-day safety follow-up visit. New and clinically significant abnormal findings during the study should be recorded as AEs.

Patients on the pembrolizumab arm will have a targeted physical examination as directed by disease, signs, and symptoms performed on Days 8 and 15 of each cycle through cycle 4 and at the 30-day safety follow-up visit. New and clinically significant abnormal findings during the study should be recorded as AEs. Beginning with cycle 5, patients on the pembrolizumab arm are only required to have an in person visit on Days 8 and 15 if clinically indicated therefore the Investigator or qualified designee will contact the patient via a phone call on Days 8 and 15 to evaluate their general health status and monitor for new AEs and concomitant medications.

7.8.2 Clinical Laboratory Parameters

The hematology panel will consist of complete blood count (hemoglobin, hematocrit, erythrocytes [i.e., red blood cell count], and leukocytes [i.e., white blood cell count]) with differential (i.e., basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts.

The clinical laboratory tests are listed in Table 4; the timing and frequency of the laboratory tests are provided in the SoA (Section 8.1). These assessments should be performed at the local laboratory associated with the Investigator site.

Table 4: Clinical Laboratory Tests

Hematology	Chemistry	Coagulation	Urinalysis	Pregnancy Test	Other
Hemoglobin	ALT	INR	Urine dipstick for blood, protein, glucose	For female patients of childbearing potential, serum or urine	Thyroid Function Tests: TSH, free T4, free T3
Hematocrit	AST	aPTT or PTT			
WBC (with differential)	Alkaline phosphatase				
Neutrophils	Sodium				
Lymphocytes	Potassium				HBV and/or HCV viral load**
Monocytes	Magnesium				
Eosinophils	Chloride				
Basophils	Total calcium				Morning, cortisol*
RBC count	BUN or Urea				
Platelets	Creatinine				ACTH*
	Glucose (non-fasted)				HIV viral load**
	Total bilirubin				
	Albumin				
	Phosphorous **(or phosphate)				
	LDH				
	Amylase**				
	Lipase**				
	Bicarbonate (or carbon dioxide)				
	Uric acid**				

* Morning, cortisol required at screening and when clinically indicated (adrenal insufficiency suspected). Blood sample should be drawn with ACTH.
** To be obtained only as clinically indicated for eligibility and throughout the study.
Abbreviations: ACTH = adrenocorticotropic hormone; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; LDH = lactate dehydrogenase; RBC=red blood cell; TSH = thyroid-stimulating hormone; WBC = white blood cell

7.8.3 Vital Signs, Height, and Weight

Vital signs include temperature, pulse, respiratory rate, blood pressure, and oxygen saturation. Weight should be assessed at the beginning of each cycle, per the SoA (Section 8.1). Height will be measured at screening only.

7.8.4 Electrocardiogram

A standard 12-lead ECG in triplicate will be performed using local standard procedures as specified in the SoA (Section 8.1). Three consecutive 12-lead ECGs (triplicates) will be performed approximately 2 minutes apart to determine mean QTc (average of triplicates). If

the mean QTc is prolonged (>500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation and should be repeated as clinically indicated. Additional triplicate ECGs may be performed as clinically indicated. Clinically significant findings seen on follow-up ECGs should be recorded as AEs.

7.8.5 ECOG Performance Status

ECOG performance status (Appendix 1) will be assessed as specified in the SoA (see Section 8.1).

7.9 Adverse Events

7.9.1 Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a patient administered a medicinal product that does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the study (investigational) product. This includes an exacerbation of pre-existing conditions or events, concurrent illnesses, drug interactions, or the significant worsening of the indication under investigation. Anticipated fluctuations of pre-existing conditions, including the disease under study that does not represent a clinically significant exacerbation or worsening, need not be considered AEs.

Symptoms of the disease under study/lack of efficacy/cancer progression should not be classified as an AE if they are within the normal day-to-day fluctuation or expected progression of the disease.

It is the responsibility of the Investigator to document all AEs that occur during the study. AEs should be reported on the appropriate eCRF.

7.9.2 Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence at any dose (including those occurring after the ICF is signed and before dosing) that:

- Results in death
- Is life-threatening (patient is at immediate risk of death from the event as it occurred)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Meets criteria for an important medical event, as described below

Important medical events that may not result in death, are not immediately life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events

include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For SAE reporting purposes, hospitalization is defined as inpatient hospital stay. Hospitalizations for elective surgery or other medical procedures that are not related to a treatment-emergent adverse event (TEAE) are not considered SAEs. Hospitalization that, in the opinion of the Investigator, is unrelated to the study treatment(s) and due to purely non-medical circumstances (e.g., respite care, lack of a caretaker at home, lack of transportation home) is also not considered to be an SAE.

Death should not be considered an SAE. The primary reason for a patient's death should be reported as the SAE, with death reported as the outcome.

7.9.3 Severity of Adverse Events

The severity of the AE will be graded according to the CTCAE v5.0. Only AEs not listed in the CTCAE should be graded as summarized in Table 5.

Table 5: CTCAE AE Grading

CTCAE Grade	Equivalent To:	Definition
Grade 1	Mild	Discomfort noticed but no disruption of normal daily activity
Grade 2	Moderate	Discomfort sufficient to reduce or affect daily activity; no treatment or medical intervention is indicated, although this could improve the overall well-being or symptoms of the patient
Grade 3	Severe	Inability to work or perform normal daily activity; treatment or medical intervention is indicated to improve the overall well-being or symptoms; delaying the onset of treatment is not putting the survival of the patient at direct risk
Grade 4	Life-threatening/ disabling	An immediate threat to life or leading to a permanent mental or physical condition that prevents work or performing normal daily activities; treatment or medical intervention is required to maintain survival
Grade 5	Death	AE resulting in death

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events

7.9.4 Relationship of Adverse Events to Study Treatment

For each AE/SAE, a causality assessment must be provided by the Investigator. The Investigator will use clinical judgment to determine whether or not an AE/SAE was related to each study treatment, as outlined below.

Related is defined as one of the following:

- **Definitely related**: This applies when, after careful medical consideration, there is almost no consideration of other causation.
- **Probably related**: There is a clinically plausible time sequence between onset of the AE and study treatment administration. The AE is unlikely to be caused by a concurrent or underlying illness, other drugs, or procedures. If applicable, the AE follows a clinically consistent resolution pattern upon withdrawal of study treatment.
- **Possibly related**: There is a clinically plausible time sequence between onset of the AE and study treatment administration, but the AE could also have been caused by the concurrent or underlying illness, other drugs, or procedures. Information regarding study treatment withdrawal may be lacking or unclear. "Possible" should be used when study treatment administration is one of several biologically plausible causes of the AE.

Not Related is defined as one of the following:

- **Unlikely related**: The AE is most likely due to a cause not related to study treatment administration. However, association with the study treatment cannot be completely ruled out.
- **Unrelated**: Another cause of the AE is most plausible, and a clinically plausible temporal sequence is inconsistent with the onset of the AE and study treatment administration and/or a causal relationship is considered biologically implausible.

For the purpose of regulatory reporting requirements, causal relationships of definite, probable, and possible will be considered treatment-related, while unlikely and unrelated will be considered not treatment-related.

7.9.5 Clinical Laboratory Adverse Events

A clinical laboratory AE is any laboratory value that is deemed clinically significant by the Investigator and is accompanied by one of the following:

- Requires a medical intervention
- Requires a modification or interruption of study treatment
- Is accompanied by clinical symptoms

Laboratory abnormalities that do not require medical intervention should not be recorded as AEs and will be captured and reported in the laboratory section of the clinical study report (CSR). If a medical intervention occurs, it should be recorded as a treatment with the abnormal laboratory finding as the AE (e.g., anemia with treatment required and blood transfusion recorded as a procedure, hyperglycemia with treatment required and change in insulin dose recorded on the concomitant medications eCRF).

The Investigator should decide, based upon the AE criteria and the clinical condition of the patient, whether a change in a laboratory parameter is clinically significant and therefore represents an AE.

If, at the end of the treatment phase with the study treatment, there are pathological laboratory values that were not present at baseline, further clinical or laboratory investigations should be performed until the values return to within reference range or until a plausible explanation (i.e., concomitant disease) is found for the pathologic laboratory values.

7.9.6 Reporting of Adverse Events and Serious Adverse Events

Patients will be monitored for all AEs from the time the first dose of study treatment is administered through 30 days after the last dose of study treatment and 90 days after the last dose of pembrolizumab. All AEs/SAEs occurring through the reporting period (30 days after last dose of danvatirsen or 90 days after last dose of pembrolizumab, which ever is longer) or until the time the patient begins a new anticancer treatment are reported in the CRF irrespective of causality. All AEs and SAEs that occur from the signing of the ICF until the first dose of study treatment should be recorded in the eCRF only if the event was related to a study procedure.

All patients with treatment-related AEs/SAEs should be observed until resolution or stabilization of the event. Any SAE occurring after the reporting period must be promptly reported if a causal relationship to the study treatment(s) is suspected.

Elective or previously scheduled hospitalizations for pre-existing conditions that have not worsened after initiation of treatment should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE.

All AEs should be recorded individually unless, in the opinion of the Investigator, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be reported rather than each individual sign or symptom. 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 as an AE or SAE, as appropriate, on the relevant form(s) (SAE Report Form and/or AE form). If a diagnosis is subsequently established, it should be reported as follow-up information becomes available. If a diagnosis is determined after the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

In general, disease progression should not be reported as an AE (or an SAE) or cause of death in this study. Instead, the AEs (or SAEs) considered as complications of disease progression should be reported. However, if no specific complications of disease progression can be identified that explain the clinical observations, “disease progression” may be reported as an SAE or cause of death.

Each AE will be evaluated for duration, severity according to the CTCAE v5.0, seriousness, and causal relationship to each study treatment. The action taken with each study treatment and the outcome must also be recorded.

All SAEs, regardless of relationship to each study treatment, must be reported immediately (within 24 hours of awareness of event by Investigator) to the Sponsor and contract research organization (CRO) pharmacovigilance group. All SAE notifications should be made by completing the AE eCRF in the electronic data capture (EDC) system. Follow-up SAE reports must be submitted by the Investigator as new information becomes available.

The Medical Monitor for this study may be contacted for advice or assistance. Contact details will be provided separately in a study contact list.

7.9.7 Regulatory Aspects of Adverse Event Reporting

The Sponsor and/or sponsor's designee is responsible for submitting reports of SAEs associated with the use of the study treatments to the appropriate regulatory authority (e.g., the US FDA), Investigators, and central IRB/EC in accordance with all applicable regulations and guidelines.

It is the responsibility of the Investigator to notify their local IRB of SAEs that occur at his or her site per IRB requirements. Investigators will be notified of all suspected unexpected serious adverse reactions (SUSARs, i.e., via 7-/15-Day Safety Reports) that occur during any clinical studies of danvatirsen. Each site is responsible for notifying their local IRB of these additional SUSARs in accordance with local regulations.

7.9.8 Pregnancy

Any pregnancy must be reported to the Sponsor or designee within 24 hours of the Investigator's knowledge of the pregnancy using a Pregnancy Report Form.

Pregnancy is not considered an AE unless there is cause to believe that the study treatments may have interfered with the effectiveness of a contraceptive medication or if the outcome of the pregnancy meets SAE criteria (miscarriage or congenital anomaly/birth defect, etc.), in which case it should be reported in the same manner and timelines as an SAE. In addition, any infant death or congenital anomaly that the Investigator suspects is related to in utero exposure to the study treatments should also be reported as an SAE. Hospitalization for normal delivery of a healthy newborn is not an SAE.

Pregnancies occurring in patients during the study treatment period and until 30 days after the patient's last dose of study treatments are considered immediately reportable events. If a pregnancy occurs in a patient, study treatments must be discontinued immediately. The pregnant woman should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. The Investigator will observe the pregnant woman until completion of the pregnancy and must notify the Sponsor of the outcome within 24 hours of the Investigator's knowledge of the pregnancy outcome. This notification includes pregnancies resulting in live, "normal" births.

If a male patient impregnates his female partner, the study personnel at the site should be informed immediately and the pregnancy reported to the Sponsor.

7.9.9 Overdose

For danvatirsen and/or pembrolizumab, administration of doses significantly exceeding those specified in the protocol (>10% above the specified dose) may be considered to be an overdose. In all cases, Investigators should be advised that any patient who receives a higher dose than that intended should be monitored closely, managed with appropriate supportive care, and followed up expectantly. There is currently no specific treatment in the event of an overdose of study drugs. All overdoses or medication errors should be reported to the Sponsor within 24 hours.

An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF.

7.10 Pharmacokinetic Assessments

Venous blood samples for determination of danvatirsen concentrations in plasma will be taken at the times presented in Table 7. All patients in the danvatirsen + pembrolizumab arm will have sparse PK samples collected at Cycle 2 Day 1, Cycle 5 Day 1, and EOT. For 10 US patients in the danvatirsen + pembrolizumab arm who are participating in the intense PK subset, additional samples will be collected at Cycle 1 Day 1 and Cycle 1 Day 5. The date and time of collection of each sample will be recorded.

PK parameters will be determined for danvatirsen. Possible relationships between PK and pharmacodynamic variables, efficacy, and/or selected toxicities will be explored, as appropriate.

Blood samples should be collected from the arm opposite from the investigational drug infusion, or from another site if collected within 24 hours of dosing.

Retained/residual PK samples may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study. This includes their use in the development and/or validation of bioassays.

Please refer to the Laboratory Manual for details on collection and processing of blood PK samples.

7.11 Immunogenicity Assessments

Venous blood samples for the assessment of ADA levels will be drawn at the timepoints presented in Table 8 from patients receiving danvatirsen + pembrolizumab. The date and time of collection of each sample will be recorded.

Blood samples should be collected from the arm opposite from the investigational drug infusion, or from another site if collected within 24 hours of dosing.

Retained/residual ADA samples may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study. This includes their use in the development and/or validation of bioassays.

Please refer to the Laboratory Manual for details on collection and processing of blood ADA samples.

7.12 Pharmacodynamic and Biomarker Assessments

Whole blood samples and tissue specimens are to be collected according to the SoA (Section 8.1).

7.12.1 Tissue Samples

An FFPE archival or fresh tumor sample collected during screening is required prior to randomization.

- Tissue samples will be used to assess pharmacodynamic activity of danvatirsen and exploratory biomarker assessments.
- Tumor tissue from a fresh biopsy (in FFPE) is preferred at screening if safe/feasible to obtain and consented to by the patient. If surgical resection of an accessible tumor is possible, then in addition to a piece of the tumor going to FFPE, 2 frozen pieces of the resection biopsy should be taken (1 each for RNA and protein analysis).
- If a fresh biopsy is not safe/feasible or not consented to by the patient, an archival sample may be provided.
    - If an archival sample is provided, it should be from the most recent biopsy of a tumor lesion within the previous 24 months collected either at the time of or after the diagnosis of advanced or metastatic disease and from a site not previously irradiated. Approximately 10 to 20 slides of freshly prepared unstained 5-micron sections from the tumor block must be provided.

For US patients only that consented to the optional tissue study, additional fresh tumor samples are requested as soon as possible after Cycle 2 Day 1 (i.e., after study treatment has been administered) and at EOT, if safe/feasible to obtain. These tumor samples will be used to further define the tissue/plasma ratio of danvatirsen and evaluate the effects of danvatirsen on the levels of STAT3 expression (RNA and/or protein) and potentially other gene expression in STAT and related pathways.

Tissue samples will be sent to a central laboratory or another facility approved by the Sponsor for analysis and storage.

See the study Laboratory Manual for further guidance on tissue collection requirements and instructions.

7.12.2 Biomarker Blood Samples

Whole blood samples will be collected for evaluation of exploratory biomarkers. The following samples for biomarker research are required:

- **Whole blood samples (All patients):** Whole blood will be collected at the timepoints specified in Table 8 to evaluate the effects of danvatirsen on the level of STAT3 expression and other gene expression.
- **Whole blood samples for isolation of peripheral blood mononuclear cells (PBMCs) (US only):** Whole blood will be collected at the timepoints specified in Table 8 to evaluate the effects of danvatirsen on the level of STAT3 expression and potentially other gene expression in PBMCs.
- **Whole blood samples for serum (US only) and plasma biomarkers (All patients):** Whole blood will be collected at the timepoints specified in Table 8 to evaluate the effects of danvatirsen on the level of circulating cytokines and other proteins.

Samples for exploratory biomarkers will be sent to a central laboratory or another facility approved by the Sponsor for storage and analysis. See the study Laboratory Manual for further guidance on blood sample collection requirements and instructions.

7.12.3 Storage and Destruction of Biological Samples

Biological samples used for PK, pharmacodynamic, ADA, and biomarker analysis may be retained at a central laboratory or another facility approved by the Sponsor until research and development of danvatirsen is completed, after which the samples will be destroyed.

Residual unused samples may be retained at a central laboratory or another facility approved by the Sponsor indefinitely as they may be used to support further bioassay or biomarker development for danvatirsen. Samples will be destroyed after use or at such time they are not needed for further research.

8 ASSESSMENTS AND PROCEDURES BY STUDY VISIT

The timing of the study assessments and procedures are summarized in the Schedule of Activities (Table 6).

8.1 Schedule of Activities

Table 6: Schedule of Activities

Assessments	Screening	Cycle 1				Cycle 2			Cycle 3 & Cycle 4			Cycle 5 and Subsequent Cycles Danvatirsen+ Pembrolizumab arm			Cycle 5 and Subsequent Cycles Pembrolizumab arm			EOT[a] (+7D)	Safety Follow-up[b] 30D (+7D)	Safety Follow-up[b] 90D (+7D)	Survival Follow-up Q12W (±7D)
	-28 to 0	D1	D3[r]& D5 + -1D	D8 ± 3D	D15 ±3D	D1 ± 3D	D8 ± 3D	D15 ± 3D	D1 ± 3D	D8 ± 3D	D15 ± 3D	D1 ±3D	D8 ±3D	D15 ±3D	D1 ±3D	D8 ±3D[s]	D15 ±3D[s]				
Informed consent[c]	X																				
Demography; baseline characteristics; medical, surgical, and cancer history	X																				
Tumor tissue collection[d]	X					X												X			
Randomization following final confirmation of eligibility[e]		X																			
Complete physical examination[f]	X	X				X			X			X			X			X			
Targeted physical examination[f]				X	X		X	X		X	X		X	X					X		
ECOG performance status	X	X				X			X			X			X			X	X		
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X		
Height	X																				
Weight[f]	X					X			X			X			X			X	X		
12-Lead ECG in triplicate	X																	X			

Assessments	Screening	Cycle 1				Cycle 2			Cycle 3 & Cycle 4			Cycle 5 and Subsequent Cycles Danvatirsen+ Pembrolizumab arm			Cycle 5 and Subsequent Cycles Pembrolizumab arm			EOT[a] (+7D)	Safety Follow-up[b] 30D (+7D)	Safety Follow-up[b] 90D (+7D)	Survival Follow-up Q12W (±7D)
	-28 to 0	D1	D3[r]& D5 + -1D	D8 ± 3D	D15 ±3D	D1 ± 3D	D8 ± 3D	D15 ± 3D	D1 ± 3D	D8 ± 3D	D15 ± 3D	D1 ±3D	D8 ±3D	D15 ±3D	D1 ±3D	D8 ±3D[s]	D15 ±3D[s]				
Laboratory safety tests (hematology)[f]	X	X		X	X	X	X	X	X	X	X	X	X	X	X			X	X		
Laboratory safety tests (serum chemistry)[f]	X	X		X	X	X	X	X	X	X	X	X			X			X	X		
Laboratory safety tests (coagulation)[f]	X	X				X			X			X			X			X	X		
Urinalysis[f]	X	X				X			X			X			X			X	X		
Thyroid function tests[f]	X	X				X			X			X			X			X	X		
Pregnancy test[h]	X	X				X			X			X			X			X	X	X	
Concomitant medications[i]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X[s]	X[s]	X	X		
AE[i]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X[s]	X[s]	X	X	X	
Tumor assessments[j]	X								X			X			X			X			
Danvatirsen[k]		X	X	X	X	X	X	X	X	X	X	X	X	X							
Pembrolizumab[l]		X				X			X			X			X						
Sparse Pharmacokinetics[m]						X						X						X			
Intense Pharmacokinetics[m]		X	X																		
ADA[n]		X				X						X						X			
US patients only whole blood, serum, and plasma biomarkers[o]		X		X	X	X			X			X			X			X			

Assessments	Screening	Cycle 1				Cycle 2			Cycle 3 & Cycle 4			Cycle 5 and Subsequent Cycles Danvatirsen+ Pembrolizumab arm			Cycle 5 and Subsequent Cycles Pembrolizumab arm			EOT[a] (+7D)	Safety Follow-up[b] 30D (+7D)	Safety Follow-up[b] 90D (+7D)	Survival Follow-up Q12W (±7D)
	-28 to 0	D1	D3[r]& D5 + - 1D	D8 ± 3D	D15 ±3D	D1 ± 3D	D8 ± 3D	D15 ± 3D	D1 ± 3D	D8 ± 3D	D15 ± 3D	D1 ±3D	D8 ±3D	D15 ±3D	D1 ±3D	D8 ±3D[s]	D15 ±3D[s]				
ROW patients only whole blood and plasma biomarkers[p]		X				X						X			X			X			
US patients only PBMC biomarkers[q]		X		X	X	X			X			X			X			X			
Survival status and anticancer therapy																		X	X		X

Abbreviations: ADA = anti-drug antibody; AE = adverse event; C = cycle; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; ICF = informed consent form; IRT = Interactive Response Technology; PBMC = peripheral blood mononuclear cell; PD = progressive disease; PK = pharmacokinetic; Q3W = every 3 weeks; Q12W = every 12 weeks; SAE = serious adverse event

a. EOT assessments need not be repeated if performed within the previous 14 days (or 30 days for imaging). When the last study visit is the same as the EOT visit, default to the EOT and consider any additional procedures unscheduled.

b. The 30-day safety follow-up visit will occur 30 days (+7 days) after the last dose of study treatment or prior to the start of new anticancer therapy, whichever occurs first. The 90-day safety follow-up may be a telephone communication or clinic visit, at the Investigator's discretion, and will occur 90 days (+7 days) after the last dose of pembrolizumab or before initiation of new anticancer therapy, whichever occurs first.

c. Informed consent may be obtained any time prior to screening procedures. There is no defined visit window between the date of ICF and C1D1.

d. Fresh tumor biopsies are requested if safe/feasible at baseline before treatment, and for US patients that consented to the optional tissue study as soon after C2D1 treatment as possible, and at EOT, but this is not a requirement. If a fresh biopsy is not safe/feasible or not consented to by the patient, an archival sample must be provided during screening.

e. Randomization via the IRT may be performed prior to C1D1 to allow for scheduling and study treatment preparation.

f. To facilitate scheduling of predose assessments, a window of −2 days is allowed to obtain the following procedures prior to dosing a patient: physical examination, weight, laboratory safety tests (hematology, serum chemistry, and coagulation), urinalysis, and thyroid function tests.

g. Vital signs include temperature, pulse, respiratory rate, blood pressure, and oxygen saturation.

h. For female patients of childbearing potential, serum or urine. The pregnancy test at the 90 day safety follow up visit is required for all patients in the UK and as clinically indicated for all other patients.

i. Patients are to be followed up for 30 days (+7 days) after the last dose of study treatment for any new reports of AEs, SAEs, and concomitant medications. Tracking of AEs will continue for all patients treated with pembrolizumab for 90 days (±7 days) after the last dose of pembrolizumab or until the initiation of subsequent anticancer therapy.

j. Tumor assessments performed within 30 days of C1D1 may be used as the baseline tumor assessments. Tumor assessments will be performed every 6 weeks until tumor progression. Patients who discontinue treatment for reasons other than PD will continue to undergo tumor assessments every 6 weeks until PD or the initiation of new anticancer therapy. To facilitate scheduling of tumor assessments, a window of ±7 days is allowed.
k. For C1 Week 1, danvatirsen will be administered on D1, D3, and D5 as a loading dose period. Starting with C1 Week 2, danvatirsen will be administered every week on D1, D8, and D15 of each treatment cycle; doses will have a ±2-day dosing window.
l. For pembrolizumab, a window of ±7 days is allowed for dosing days. Patients will receive pembrolizumab Q3W on D1 of each cycle.
m. For C1 Week 1, intense PK sampling will be performed on D1 and D5 for 10 US patients in the danvatirsen + pembrolizumab arm. Sparse PK sampling also occurs on C2D1, C5D1 and EOT for all patients in the danvatirsen + pembrolizumab arm. Detailed PK sampling times are provided in Table 7.
n. ADA will be assessed for danvatirsen + pembrolizumab patients at C1D1, C2D1, C5D1, and EOT, as shown in Table 8.
o. Whole blood will be collected for the assessment of whole blood, serum, and plasma biomarkers in all US patients at C1D1, D8, and D15; C2D1; C3D1; C5D1; and EOT, as shown in Table 8.
p. Whole blood will be collected for the assessment of whole blood and plasma biomarkers in all ROW patients at C1D1; C2D1; C5D1; and EOT, as shown in Table 8.
q. Whole blood will be collected for assessment of PBMC biomarkers in all US patients at C1D1, D8, and D15; C2D1; C3D1; C5D1; and EOT, as shown in Table 8.
r. C1D3 and C1D5 visits are only applicable to patients on the danvatirsen + pembrolizumab arm. A minimum of one day is required between the D1, D3 and D5 danvatirsen doses. Note: The visit windows on D1, D3 and D5 do not apply to patients that are participating in the intense PK subset.
s. D8 and D15 AE and concomitant medication assessments for patients on the pembrolizumab arm, may be conducted via a phone call beginning with Cycle 5. In person visits should occur as clinically indicated.

8.2 Pharmacokinetic, Immunogenicity, and Biomarker Sampling

Table 7: Pharmacokinetic Sampling

Timepoint		PK Sample	
Cycle	**Day**	**10 Danvatirsen + Pembrolizumab US Patients**	**All Other Danvatirsen + Pembrolizumab Patients**
1	1	Predose and at 0.5 h (±5 min), 1 h (end of infusion; ±10 min), 2 h (±15 min), 4 h (±30 min), and 6 h (±30 min) after the start of the danvatirsen infusion	
1	5	Predose and at 0.5 h (±5 min), 1 h (end of infusion; ±10 min), 2 h (±15 min), 4 h (±30 min), and 6 h (±30 min) after the start of the danvatirsen infusion	
2	1	Predose and 2 h (±15 min) after the start of the danvatirsen infusion	Predose and 2 h (±15 min) after the start of the danvatirsen infusion
5	1	Predose and 2 h (±15 min) after the start of the danvatirsen infusion	Predose and 2 h (±15 min) after the start of the danvatirsen infusion
EOT	EOT	Any time during the EOT visit	Any time during the EOT visit

Abbreviation: PK = pharmacokinetic

Table 8: Immunogenicity and Biomarker Sampling

Timepoint		Immunogenicity Sample	Whole Blood, Serum, and Plasma Biomarker Sample	PBMC Biomarker Sample	Whole Blood and Plasma Biomarker Sample
Cycle	**Day**	**All Danvatirsen + Pembrolizumab Patients**	**US Patients**	**US Patients**	**ROW Patients**
1	1	X (Predose)	X (Predose)	X (Predose)	X (Predose)
1	8		X	X	
1	15		X	X	
2	1	X	X	X	X
3	1		X	X	
5	1	X	X	X	X
End of Treatment		X	X	X	X

Abbreviation: PBMC = peripheral blood mononuclear cell

9 STATISTICAL CONSIDERATIONS

A summary of the study design and the planned statistical analyses for the primary and key secondary endpoints is presented below. A more technical and detailed description of the statistical methodology will be documented in the statistical analysis plan (SAP). Changes to the analyses will be described and justified in the CSR for the study.

9.1 Statistical Hypotheses

The primary efficacy evaluation will be the magnitude of ORR in each of the treatment arms and the probability that the combination arm ORR is superior to that of the control (monotherapy) arm, that is $Pr(ORR_{comb} > ORR_{con} \mid data)$.

9.2 Sample Size

Sample size considerations were based on monitoring the primary efficacy endpoint, ORR, using a 2-arm Bayesian optimal phase 2 (BOP2) design (Zhao et al 2022).

Specifically, let n denote the interim sample size and N denote the maximum sample size. Let ORR_{con} denote the control ORR and ORR_{comb} denote the combination treatment ORR. We define the null hypothesis H_0: $ORR_{comb} \leq ORR_{con}$, under which the combination arm is deemed as unacceptable, respective to the control. We employ the following Bayesian rule to make a go/no-go decision:

(Futility stopping) stop enrolling patients and claim that the experimental arm is unacceptable if:

$$Pr(ORR_{comb} > ORR_{con}|data) < \lambda(\frac{n}{N})^{\alpha},$$

Where λ=0.96 and α=0.94 are design parameters optimized to maximize the power under H_0:ORR_{con} = 0.15 and ORR_{comb} = 0.43, while controlling the type I error rate at 0.05 under ORR_{con} = ORR_{comb} = 0.15. This optimization is performed assuming a vague prior Beta(0.5,0.5) for ORR_{con} and ORR_{comb}.

An interim futility analysis is planned when ORR can be assessed for the first 39 patients, and the final ORR analysis is planned after 81 patients are followed for a minimum of 3 months (2 radiologic scans). A 2:1 combination:control randomization will be used for the 2 arms and will yield 83% power at the 1-sided 5% alpha based on the above decision rule to reject the null hypothesis and conclude that the combination arm is superior compared to the control:

At the interim analysis: $Pr(ORR_{comb} > ORR_{con} \mid \text{data}) > 0.5$, and
At the final analysis: $Pr(ORR_{comb} > ORR_{con} \mid \text{data}) > 0.96$

The go/no-go criteria, also presented in detail in Table 9 below, are non-binding.

The operating characteristics of the design, based on 100000 simulations using the BOP2 application, are presented in Table 10.

Table 9: Optimized Stopping Boundaries

Control N	Combination N	# CR/PR in Control	Stop for Futility if # of CR/PR in Combination - # of CR/PR in Control ≤
13	26	0	0
13	26	1~2	1
13	26	3	2
13	26	4	3
13	26	5	4
13	26	6	5
13	26	7	6
13	26	8	7
13	26	9	8
13	26	10	9
13	26	11	10
13	26	12	11
13	26	13	12
27	54	0	4
27	54	1	7
27	54	2	10
27	54	3	11
27	54	4	13
27	54	5	15
27	54	6	16
27	54	7	17
27	54	8	18
27	54	9	20
27	54	10	21
27	54	11	22
27	54	12~13	23
27	54	14	24
27	54	15	25
27	54	16~17	26
27	54	18~19	27
27	54	20~26	28
27	54	27	27

Abbreviations: CR = complete response; PR = partial response

Table 10: Operating Characteristics

Scenario	% ORR Control	% ORR Combination	Early Futility Stopping (%)	Claim Promising (%)	Average Sample Size
1	15	15	46.1	4.6	62
2	23	23	43.8	4.5	63
3	20	40	7.1	54.6	78
4	23	43	7.7	52.9	78
5	25	50	4.5	68.6	79
6	15	43	1.9	82.7	80

Abbreviation: ORR = objective response rate

Additional futility monitoring criteria will be taken into consideration for the subgroup of patients with CPS ≥1 and <20. Specifically, if no more than one patient achieves a response (confirmed or unconfirmed CR or PR within the first two scans) in the first 10 patients enrolled in the combination arm for this subgroup, there will be no further enrollment in this subgroup, and the study will continue to enroll in the CPS ≥20 subgroup, consistent with any guidance based on the monitoring criteria outlined in Table 9. Additionally, accrual in the CPS ≥1 and <20 subgroup will pause, if no responses have been achieved, but response data for the first 10 patients in that subgroup are not yet mature, defined as at least 2 scans assessed.

Considering the limited size of the CPS ≥1 and <20 subgroup, the futility criteria were derived based on a single arm BOP2 design with the interim assessment after 10 patients, a final assessment of 27 patients (half of the intended size of the combination arm) testing a null hypothesis of 15% ORR (KEYNOTE-048 pembrolizumab monotherapy ORR for this subgroup (Burtness et al 2022)) vs. an alternative hypothesis of 29% ORR (SCORES combination arm for this subgroup), at 1-sided 10% level with approximately 65% power.

9.3 Analysis Populations

9.3.1 Full Analysis Set

The Full Analysis Set (FAS) will include all patients who receive at least 1 dose of study treatment based on the treatment assigned at randomization and will be the primary analysis set for efficacy analyses.

9.3.2 Safety Analysis Set

The Safety Analysis Set (SAS) will include all patients who receive at least 1 dose of study treatment based on the actual treatment received and will be the primary analysis set for safety analyses.

9.3.3 PK Evaluable Set

The PK Evaluable Set will include all FAS patients with evaluable PK data.

9.3.4 Biomarker Evaluable Set

The Biomarker Evaluable Set will include all FAS patients with evaluable biomarker data.

9.4 General Considerations

Descriptive statistics will be used to display the results. Continuous variables, including baseline characteristics, will be summarized by reporting the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical/discrete variables will be summarized using frequency tables showing the number and percentage of patients within a category.

For time-to-event endpoints, the median, 25th and 75th percentiles (if estimable) using Kaplan-Meier methods along with the 90% and 95% confidence intervals (CIs) will be reported. Kaplan-Meier curves will also be generated for each time-to-event endpoint.

Missing data will not be imputed except as described in the SAP. Baseline value will be defined as the last non-missing value before receipt of the first dose of study treatment.

9.5 Disposition, Demographic and Baseline Characteristics, and Exposure

The number of patients in each study population and the reasons for exclusion will be summarized.

Patient demographics, baseline characteristics, and exposure will be listed and summarized for the FAS. Patient attributes will be summarized using frequency distributions for categorical variables or descriptive statistics for continuous endpoints, as appropriate.

Descriptive information for danvatirsen and pembrolizumab will be provided regarding the number of doses administered, the number of dose modifications and delays, the duration of treatment, and the relative dose intensity (% of treatment administered compared to targeted).

9.6 Analysis of Safety

The analysis of safety will focus on AEs with summaries of TEAEs (i.e., AEs that start or increase in severity after the first dose of study treatment). AEs will be coded according to the latest Medical Dictionary for Regulatory Activities (MedDRA) version available at the time of database creation. The severity of AEs will be graded according to NCI CTCAE v5.0.

The number and percent of patients with any AE will be tabulated by system organ class and preferred term using MedDRA. AEs related to danvatirsen, AEs related to pembrolizumab, all SAEs, related SAEs, and AEs by maximum CTCAE grade will be summarized similarly.

Laboratory test results after the first dose of study treatment will be summarized by shift in CTCAE grade for laboratory parameters that can be graded. Laboratory parameters that cannot be graded by CTCAE will be summarized by shifts to low, normal, or high postbaseline.

Vital signs will be summarized by the change from baseline at each postbaseline timepoint. Descriptive statistics will be provided by study visit for physical examination, ECOG performance status, ECG, and weight parameters.

9.7 Analysis of Efficacy

The primary efficacy analysis for ORR, as well as the interim analysis for PFS and OS, will be conducted once all patients are treated and followed for a minimum of 3 months (2 radiologic scans). The final analysis for PFS and OS will be conducted after all patients have been followed for a minimum of 15 months, unless the study is deemed futile at the interim or primary analysis stage.

The overall response will be assessed by the Investigator based on the RECIST v1.1 criteria at each timepoint specified the SoA (Section 8.1). The best overall response (BOR) will be assessed from response assessments occurring after the first dose of either study treatment up to the first documented assessment of PD that is prior to the initiation of a new anticancer therapy. Objective response (i.e., BOR of PR or CR) will require confirmation of the response (CR or PR) at least 4 weeks after the initial CR or PR.

The ORR will be defined as the proportion of patients with a confirmed objective response as assessed by the Investigator in the FAS. Patients who receive at least one dose of either study treatment but have no valid postbaseline radiographic assessment will be considered non-responders. The ORR will be reported along with the corresponding 2-sided 90% and 95% Clopper-Pearson exact CI. The criteria for promising ORR at the primary analysis are detailed in Table 9 and, in addition, a comparison between the 2 treatment groups will be performed based on Fisher's exact test.

DOR is defined as the date of the patient's first confirmed BOR of CR or PR to the earliest date of documented progression or death if no prior evidence of disease progression, for all patients in the FAS with a confirmed objective response. A patient that starts a new anticancer therapy prior to disease progression will be censored at the date of last valid disease assessment prior to the start of the new anticancer therapy. All other patients without progression or death will be censored at the date of the last valid disease assessment. DOR will be summarized using Kaplan-Meier methods.

The DCR, which includes a BOR of CR, PR, or SD, will be analyzed similar to ORR.

PFS is defined as the time from randomization to the first of either disease progression or death from any cause, where disease progression will be determined based on RECIST v1.1 criteria. A patient that starts a new anticancer therapy prior to disease progression will be censored at the date of last valid disease assessment prior to the start of the new anticancer therapy. Patients without documented disease progression or death will be censored at the last valid disease assessment date. Any patient without a valid disease assessment will be censored on the day of the first dose. PFS will be summarized using Kaplan-Meier methods and compared between the 2 groups using a stratified log rank test.

Sensitivity analyses for ORR, DOR, and PFS will be repeated with the requirement of confirmation of disease progression at least 4 weeks after an initial assessment of PD. Any unconfirmed disease progression assessment will not be counted as PD in these analyses.

OS is defined as the time from randomization to death from any cause. Patients without documentation of death as of the data cutoff will be censored at the last date the patient was known alive. OS will be summarized using Kaplan-Meier methods and compared between the 2 groups using a stratified log rank test.

All efficacy analyses will be performed for two key efficacy subgroups, which includes all patients with CPS ≥20 and CPS ≥50. Additional subgroups of interest will be defined in the SAP.

9.8 Plasma Pharmacokinetic Analysis

A detailed PK analysis plan will be provided in the SAP.

The plasma concentrations of danvatirsen will be summarized by nominal sampling time using descriptive statistics. Plasma PK parameters (i.e., maximum concentration recorded [C_{max}], trough concentration [C_{trough}], area under the plasma concentration-time curve over the dosing interval [AUC_{tau}], and time to maximum plasma concentration [T_{max}]) after single and multiple doses as feasible will be listed and summarized using descriptive statistics. Mean plasma concentrations over time will be plotted in semi-logarithmic and linear scale as mean ± standard deviation.

All available PK data may be used to conduct population PK, PK/pharmacodynamic, and exposure-response analyses.

9.9 Biomarker and Immunogenicity Analysis

Descriptive analyses of ADA results may be performed based on the SAS.

Descriptive analyses, as well as correlative analyses with exposure and response, will be performed based on the Biomarker Evaluable Set, for the whole blood, serum, and plasma biomarkers collected as well as the PBMC biomarkers.

9.10 Interim Analyses

9.10.1 Safety Analysis

An internal team of experts and a subset of site Principal Investigators will constitute the Safety Review Committee, which will meet regularly to monitor the safety of the combination regimen throughout this study. The committee will consider all available clinical safety and laboratory safety data. The details on membership, key responsibilities, and corresponding procedures are provided in the Safety Review Committee charter. Cumulative safety data from the first 9 patients randomized who have completed at least one cycle of study treatment will be reviewed for any unexpected toxicities, discontinuations due to study drug-related toxicities, or other signals that may raise safety concerns. Accrual to the study will be suspended if this analysis is not completed by the time the 20th patient is randomized to the study. If the combination is deemed intolerable, further accrual will be halted.

9.10.2 Futility Analysis

The BOP2 suggested futility monitoring criteria that apply for the entire study population, as well as the CPS ≥1 and <20 subgroup, are presented in Section 9.2 and are non-binding. At the primary analysis, a lower ORR for advancement may also suffice by taking into

consideration the CR rate that suggests superiority with regard to deep responses over that observed with pembrolizumab alone.

10 ETHICAL AND LEGAL CONSIDERATIONS

10.1 Compliance Statement

This study will be conducted in accordance with the protocol and with ICH GCP guidelines, as well as all applicable country and regional legal and regulatory requirements. The Investigator is responsible for ensuring that this protocol, the site's ICF, and any other information that will be presented to potential patients are reviewed and approved by the appropriate Independent Ethics Committee (IEC)/IRB prior to the enrollment of any study patients.

10.2 Ethics Committee and Regulatory Authorities

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations

The Sponsor or designee will submit the study protocol plus all relevant study documents to applicable regulatory agencies for approval before the study start. No patient will be admitted to the study until appropriate regulatory approval of the study protocol has been received.

Each Investigator must complete a Form FDA 1572 or equivalent and provide the completed form according to written instructions to the Sponsor (or designee).

The study will be registered at www.clinicaltrials.gov and other trial registries as required based on the countries in which the study is conducted.

The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be approved by an IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/EC,

European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.3 Financial Disclosure

The 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 regulatory authorities. The Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.4 Informed Consent Process

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

Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements (where applicable), and the IRB/IEC or study site.

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

Patients will be reconsented to the most current version of the ICF(s) during their participation in the study, as necessary.

A copy of the ICF(s) must be provided to the patient or the patient’s legally authorized representative.

10.5 Patient Data Protection

Patients will be assigned a unique identifier during screening. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information that would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient who will be required to give consent for their data to be used as described in the informed consent.

10.6 Dissemination of Clinical Study Data

The Sponsor will comply with current regulatory requirements for disclosure and submission of study results. The Sponsor’s policy on publication of study results is described in Section 10.10.

10.7 Source Documents

Source data are all information, original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Electronic source data are data initially recorded in electronic form. Examples of source data include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, patients' memory aids or evaluation checklists, pharmacy dispensing records, audio recordings of counseling sessions, recorded data from automated instruments, copies or transcriptions certified after being verified as accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, X-rays, and patient files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical study.

The source documents should indicate the patient's consent to participate in the study. Data collection is the responsibility of the clinical study staff at the site under the supervision of the site Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Definition of what constitutes source data can be found in ICH guidance for industry E6 Good Clinical Practice: Consolidated Guidance.

10.7.1 Electronic Case Report Form

Data will be collected using an EDC system and eCRFs. Sites will receive training on the EDC system. All users will be supplied with unique login credentials.

For each patient enrolled, eCRFs must be completed within a reasonable time period (i.e., <2 weeks after data collection).

Full information regarding EDC and completing eCRFs is included in a study manual. All questions or comments related to electronic capture should be directed to the assigned monitor.

10.7.2 Clinical Study Report

A CSR will be prepared under the responsibility and supervision of the Sponsor and signed by a Sponsor representative, thereby indicating their agreement with the analyses, results, and conclusions of the CSR.

10.8 Quality Control and Quality Assurance

10.8.1 Data Quality Assurance

All patient data relating to the study will be recorded in the electronic eCRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The Investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents.

The monitoring plan provided describes monitoring strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies), methods, responsibilities, and requirements (including handling of noncompliance issues and monitoring techniques [i.e., central, remote, or on-site monitoring]).

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., CROs).

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 patients 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.

The Sponsor will determine the minimum retention period and, upon request, will provide guidance to the Investigator when documents no longer need to be retained. The Sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All study documents shall be made available if required by relevant regulatory authorities. The Investigator must consult with and obtain written approval by the Sponsor prior to destroying study and/or patient files.

No data should be destroyed without the agreement of the Sponsor. Should the Investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified in writing of the new responsible person and/or the new location. The Sponsor will inform the Investigator, in writing, when the study-related records are no longer needed.

Patients' medical records and other original data will be archived in accordance with the archiving regulations or facilities of the investigational site.

10.8.2 Quality Assurance Audits

Clinical centers may be audited by the Sponsor's quality unit qualified auditor or designee as required per approved schedule. The purpose of an audit, which is independent of and separate from routine monitoring or quality unit functions, is to evaluate study conduct and compliance with the protocol, standard operating procedures, ICH GCPs, and the applicable regulatory requirements. The Investigator and the Sponsor may also be subject to an inspection by US FDA, European regulatory authorities, or other applicable regulatory authorities at any time.

The auditor and regulatory authorities will require authority from the Investigator to have direct access to patients' medical records. It is important that the Investigator(s) and their staff cooperate with the auditor or regulatory authorities during this audit or inspection.

10.9 Study and Site Closure

The Sponsor or designee reserves the right to close a study site or terminate the study at any time for any reason (e.g., as necessary for patient safety) at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

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

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the Investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IRBs/ECs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow-up.

10.10 Publication Policy

The conditions regulating dissemination of the information derived from this study are described in the Clinical Trial Agreement.

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 multi-site studies only in their entirety and not as individual site data.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

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12 APPENDICES

APPENDIX 1. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

Grade	Performance Status
0	Fully active, able to carry on all predisease 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 selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Appendix 2. eGFR Formulas

Cockroft-Gault Method

For serum creatinine concentration in mg/dL:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}^{a}) \times (\text{wt}) \times 0.85 \text{ (if female), or} \times 1.0 \text{ (if male)}}{72 \times \text{serum creatinine } (mg/dL)}$$

For serum creatinine concentration in μmol/L:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}^{a}) \times (\text{wt}) \times 0.85 \text{ (if female), or} \times 1.0 \text{ (if male)}}{0.81 \times \text{serum creatinine } (\mu mol/L)}$$

Abbreviations: CrCl = creatinine clearance; wt = weight.
[a] Age in years, weight (wt) in kilograms.

Source: Cockcroft and Gault 1976

MDRD Method

GFR (mL/min/1.73 m²) = 175 × (Scr)$^{-1.154}$ × (Age)$^{-0.203}$ × (0.742 if female) × (1.212 if African American)

Scr (standardized serum creatinine) = mg/dL

Sources: Levay et al., 1999; Levay et al., 2006

APPENDIX 3. BIRTH CONTROL METHODS CONSIDERED HIGHLY EFFECTIVE

According to the Clinical Trial Facilitation Group "Recommendations related to contraception and pregnancy testing in clinical trial" (CTFG 2020), methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods, such as:

1. Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation
    - oral
    - intravaginal
    - transdermal
2. Progesterone-only hormonal contraception associated with inhibition of ovulation
    - oral
    - injectable
    - implantable
3. Intrauterine device
4. Intrauterine hormone-releasing system
5. Bilateral tubal occlusion
6. Vasectomized partner
7. Sexual abstinence

APPENDIX 4. TOXICITY GRADING AND DOSE MODIFICATION GUIDELINES FOR PEMBROLIZUMAB

Adapted from ASCO Guidelines for the Management of Immune-Related Adverse Events: h**ttps://ascopubs.org/doi/pdf/10.1200/JCO.21.01440 (**Schneider et al 2021**)**

AE and Grade by CTCAE v5.0	**Management**
Cutaneous Toxicities	
Rash or Inflammatory Dermatitis	
G1: Rash covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	• Continue pembrolizumab. • Treat with topical emollients and/or mild-moderate potency topical corticosteroids. • Counsel patients to avoid skin irritants.
G2: Rash covering 10%-30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADLs; rash covering >30% BSA with or without mild symptoms	• Consider holding pembrolizumab and monitor weekly for improvement. If skin toxicity not improved after 4 weeks, then regrade toxicity as G3. • In addition, treat with topical emollients, oral antihistamines, and medium-to-high potency topical corticosteroids. • Consider initiating prednisone (or equivalent) at dosing 0.5-1 mg/kg, tapering over 4 weeks. In patients with pruritis without rash, consider topical anti-itch remedies (e.g., refrigerated menthol, pramoxine).
G3: Rash covering >30% BSA with moderate or severe symptoms; limiting self-care ADL	• Hold pembrolizumab therapy and consult with dermatology to determine appropriateness of resuming. • Treat with topical emollients, oral antihistamines, and high-potency topical corticosteroids. May also consider phototherapy to treat severe pruritus. • Initiate oral prednisone or equivalent (1 mg/kg/d) tapering over at least 4 weeks. • Once downgraded to ≤G1 and prednisone (or equivalent) below 10 mg/d, clinicians may consider resuming pembrolizumab therapy with close monitoring and follow-up with dermatology in certain cases such as psoriasis. • In patients with pruritis without rash, may treat with gabapentin, pregabalin, aprepitant, or dupilumab.
G4: Severe consequences requiring hospitalization or urgent intervention indicated or life-threatening consequences	• Immediate hold pembrolizumab. • May admit patient immediately with direct oncology involvement and with an urgent consult by dermatology. • Systemic steroids: IV methylprednisolone (or equivalent) dosed at 1-2 mg/kg with slow tapering when the toxicity resolves. • Monitor closely for progression to SCAR.

AE and Grade by CTCAE v5.0	Management
	• Consider alternative antineoplastic therapy over resuming pembrolizumab if the skin irAE does not resolve to ≤G1.
Bullous Dermatoses	
G1: Asymptomatic or blisters covering <10% BSA and no associated erythema	• If blisters are <10% BSA, are asymptomatic and non-inflammatory (such as the case with friction blisters or pressure blisters), cessation of pembrolizumab is not necessary and only observation/local wound care is warranted. • When symptomatic bullae or erosions, which are "deroofed" vesicles or bullae, are noted on the skin or mucosal surfaces, the cutaneous irAE is considered at least G2. • See G2 management recommendations.
G2: Blistering that affects quality of life and require intervention based on diagnosis not meeting criteria for >G2. Blisters covering 10%-30% BSA	• Hold pembrolizumab and consult with dermatology for steroid-sparing options, work up, and to determine appropriateness of resuming. • Attention given to general local wound care, which includes plain petrolatum ointment and bandages or plain petrolatum ointment gauze and bandage over any open erosions, which are left on the skin after the blister has "popped" or if the roof of the blister easily sloughs off. • Initiate class 1 high potency topical steroid, e.g., clobetasol, betamethasone, or equivalent and reassess every 3 days for progression or improvement. • Low threshold to initiate treatment with prednisone (or equivalent) at 0.5-1 mg/kg/d dosing and taper over at least 4 weeks. • Monitor patients closely for progression to greater BSA involvement and/or mucous membrane involvement. Consider following patients closely using serial photography.
G3: Skin sloughing covering >30% BSA with associated pain and limiting self-care ADL	• Hold pembrolizumab and consider admitting patient. • Administer IV methylprednisolone (or equivalent) 1-2 mg/kg and when appropriate convert to oral steroids, tapering over at least 4 weeks. • If bullous pemphigoid is diagnosed, it may be possible to avoid long-term use of systemic steroids and transition to steroid-sparing options (e.g., IVIG and rituximab), as an alternative approach to treating the irAE. • Consult with dermatology to determine appropriateness of resuming pembrolizumab once symptoms improve.
G4: Blisters covering >30% BSA with associated fluid or electrolyte abnormalities	• Permanently discontinue pembrolizumab. • Admit patient immediately and place under supervision of a dermatologist.

AE and Grade by CTCAE v5.0	Management
	• Administer IV methylprednisolone (or equivalent) 1–2 mg/kg and when appropriate convert to oral steroids, with tapering over at least 4 weeks. • If bullous pemphigoid is diagnosed, it may be possible to avoid long-term use of systemic steroids and treat with steroid-sparing options as an alternative approach to treating the irAE (e.g., IVIG and rituximab).
SCAR	
All Grades	• In cases of suspected SJS or any mucous membrane involvement (not including isolated stomatitis), discontinue pembrolizumab treatment and consult dermatology. Monitor closely for improvement regardless of grade.
G1 and G2: NA	• For the SCAR adverse reactions, there are no G1 or G2 categories. If limited BSA is involved with bullae or erosions, there should remain high concern that this reaction will progress to G3 or G4.
G3: Skin sloughing covering <10% BSA with mucosal involvement-associated signs (e.g., erythema, purpura, epidermal detachment, and mucous membrane detachment)	• Hold pembrolizumab therapy and consult with dermatology. • 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. • 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 methylprednisolone (or equivalent) 0.5-1 mg/kg and convert to oral corticosteroids on response, wean over at least 4 weeks. • Given the immune mechanism of action of these medicines, use of immune suppression is warranted and should be offered. The usual prohibition of corticosteroids for SJS is not relevant here, as the underlying mechanism is a T-cell immune-directed toxicity. Adequate suppression is necessary with corticosteroids or other agents and may be prolonged in cases of DRESS or drug hypersensitivity syndrome. • For mucous membrane involvement of SJS or TEN, appropriate consulting services should be offered to guide management in preventing sequelae from scarring (e.g., ophthalmology, otolaryngology, urology, or gynecology, as appropriate).
G4: Skin erythema and blistering/sloughing covering ≥10% BSA with associated signs (e.g., erythema, purpura, epidermal detachment, mucous membrane detachment) and/or	• Permanently discontinue pembrolizumab. • 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, otolaryngology, etc.). • Initiate IV methylprednisolone (or equivalent) 1-2 mg/kg, tapering when toxicity resolves to normal.

AE and Grade by CTCAE v5.0	Management
systemic symptoms and concerning associated blood work abnormalities (e.g., liver function test elevations in the setting of DRESS or DIHS)	• IVIG or cyclosporine may also be considered in severe or steroid-unresponsive cases. • Consider pain/palliative consultation and/or admission in patients presenting with DRESS manifestations.
Colitis	
G1: Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	• Continue pembrolizumab. Alternatively, pembrolizumab may be held temporarily and resumed if toxicity does not exceed G1 or resolves. • May also include supportive care with medications such as loperamide if infection has been ruled out in patients with diarrhea only and not colitis-related symptoms as a temporary measure. • Monitor for dehydration and recommend dietary changes. • Patient should be closely monitored by phone or electronic medical system for symptoms changes by clinical providers every 3 days or more frequently if needed until stabilized. • May obtain gastroenterology consult for prolonged G1 cases and consider endoscopy with biopsies.
G2: Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline	• Hold pembrolizumab at least until recovery to G1 – see last bullets. • May also include supportive care with medications such as loperamide if infection has been ruled out in patients with diarrhea only and not colitis-related symptoms as a temporary measure. • Consider consult with gastroenterology for ≥G2. • Administer corticosteroids, unless diarrhea is transient, starting with initial dose of 1 mg/kg/d prednisone or equivalent until symptoms improve to G1, and then start taper over 4-6 weeks. • Consider adding narrower-spectrum/more potent agents, including anti-TNF (infliximab) or anti-integrin (vedolizumab) antibody to patients whose colitis is corticosteroid-refractory (i.e., no decrease by one grade in 72 hours) or dependent or with high-risk endoscopic features on initial endoscopy exam. • When symptoms improve to ≤G1, taper corticosteroids over 4-6 weeks; may consider shorter tapers in patients also treated with biologics. • Endoscopic evaluation with EGD/colonoscopy is highly recommended for cases ≥G2 to stratify patients for early treatment of biologics based on the endoscopic findings. • Resuming pembrolizumab after symptoms improve to <G1 may be considered when steroid taper is completed, risks/benefits are reviewed if maintained on biologics, and/or if endoscopic and histologic remission are achieved. Fecal calprotectin <116 µg/g may

AE and Grade by CTCAE v5.0	Management
	be considered as a surrogate for endoscopic and histologic remission.
G3: Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	• Follow G2 recommendations as listed, with the following additions for G3: • Administer corticosteroids (initial dose of 1-2 mg/kg/d prednisone or equivalent) until symptoms improve to G1, and then start taper over 4-6 weeks. Consider IV methylprednisolone, especially if concern for concurrent upper GI inflammation. • Consider early introduction of infliximab or vedolizumab in addition to steroids in patients with high-risk endoscopic features on initial endoscopy exam or inadequate response to steroids (persistent symptoms after 3 days). • Consider hospitalization for patients with dehydration or electrolyte imbalance. • Consider repeat colonoscopy in patients who are immunosuppression-refractory.
G4: Life-threatening consequences; urgent intervention indicated	• Follow G2-G3 recommendations as listed, with the following additions for G4: • Permanently discontinue treatment. • Should provide inpatient care. • Administer 1-2 mg/kg/d methylprednisolone or equivalent until symptoms improve to G1, and then start taper over 4-6 weeks. • Consider early biologics (infliximab or vedolizumab) if inadequate response to steroids after 3 days. • Consider lower GI endoscopy if symptoms are refractory despite treatment or there is concern of new infections.
Hepatitis	
G1: Asymptomatic (AST or ALT >ULN to 3.0× ULN and/or total bilirubin >ULN to 1.5× ULN)	• Continue pembrolizumab with close monitoring; consider alternate etiologies. • Consider monitoring labs 1-2 times weekly. • Manage with supportive care for symptom control.
G2: Asymptomatic (AST or ALT >3.0 to ≤5× ULN and/or total bilirubin >1.5 to ≤3× ULN)	• Hold pembrolizumab temporarily. • Patients should be advised to stop unnecessary medications and any known hepatotoxic drugs. Temporarily hold other potentially hepatotoxic oncologic agents. • For G2 hepatic toxicity, may administer steroid (0.5-1 mg/kg/day prednisone) or equivalent if no improvement is seen after 3-5 days. • Increase frequency of monitoring to every 3 days. • If inadequate improvement after 3 days, consider adding MMF.

AE and Grade by CTCAE v5.0	Management
	• May initiate steroid taper when symptoms improve to ≤G1 and may resume pembrolizumab when steroid ≤10 mg/d. Taper over at least 1 month. • Consider hepatology consult for G2 and above. • May resume if recover to ≤G1 on prednisone ≤10 mg/d.
G3: AST or ALT 5-20× ULN and/or total bilirubin 3-10× ULN, OR symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis; reactivation of chronic hepatitis	• Follow G2 recommendations as listed, with the following additions for G3: • Consider permanently discontinuing pembrolizumab if asymptomatic; permanently discontinue if symptomatic. Immediately start steroid 1-2 mg/kg methylprednisolone or equivalents. • If steroid refractory, consider liver biopsy to rule out NASH, tumor, cholestatic variants, other drug-related hepatic inflammation, infection, or other autoimmune entity and consider adding azathioprine or mycophenolate if infectious cause is ruled out. • Labs daily or every other day; consider inpatient monitoring for patients with AST/ALT >8× ULN and/or elevated total bilirubin 3× >ULN. • If no improvement is achieved with steroid or for patients on pembrolizumab combined with a novel agent, with standard chemotherapy, or with targeted therapy, refer to hepatologist for further pathologic evaluation of hepatitis. • Steroid taper can be attempted around 4-6 weeks when ≤G1, re-escalate if needed, optimal duration unclear. • Consider transfer to tertiary care facility if necessary.
G4: AST or ALT >20× ULN and/or total bilirubin >10× ULN OR decompensated liver function (e.g., ascites, coagulopathy, encephalopathy, coma)	• Follow G3 recommendations as listed, with the following additions for G4: • Administer 2 mg/kg/d methylprednisolone equivalents.
Lung Toxicities	
Pneumonitis	
G1: Asymptomatic; confined to one lobe of the lung or <25% of lung parenchyma; clinical or diagnostic observations only	• Hold pembrolizumab or proceed with close monitoring. • Monitor patients weekly with history and physical examination, pulse oximetry; may also offer chest imaging (CXR, CT) if uncertain diagnosis and/or to follow progress. • Repeat chest imaging in 3-4 weeks or sooner if patient becomes symptomatic. • In patients who have had baseline testing, may offer a repeat spirometry or DLCO in 3-4 weeks.

AE and Grade by CTCAE v5.0	Management
	• May resume pembrolizumab with radiographic evidence of improvement or resolution if held. If no improvement, should treat as G2.
G2: Symptomatic; Involves more than one lobe of the lung or 25%-50% of lung parenchyma; medical intervention indicated; limiting instrumental ADL	• Hold pembrolizumab until clinical improvement to ≤G1. • Prednisone 1-2 mg/kg/d and taper over 4-6 weeks. • Consider bronchoscopy with BAL ± transbronchial biopsy. • Consider empiric antibiotics if infection remains in the differential diagnosis after workup. • Monitor at least once per week with history and physical examination, pulse oximetry, consider radiological imaging; if no clinical improvement after 48-72 hours of prednisone, treat as G3. • Pulmonary and infectious disease consults if necessary.
G3: Severe symptoms; Hospitalization required: Involves all lung lobes or >50% of lung parenchyma; limiting self-care ADL; oxygen indicated. G4: Life-threatening respiratory compromise; urgent intervention indicated (intubation)	• Permanently discontinue pembrolizumab. • Empiric antibiotics may be considered. • Methylprednisolone IV 1-2 mg/kg/d. • If no improvement after 48 hours, may add immunosuppressive agent. Options include infliximab or MMF IV or IVIG or cyclophosphamide. Taper corticosteroids over 4-6 weeks. • Pulmonary and infectious disease consults if necessary. • May consider bronchoscopy with BAL ± transbronchial biopsy if patient can tolerate.
Endocrine Toxicities	
Thyroid	
Primary Hypothyroidism	
G1: TSH >4.5 and <10 mIU/L and asymptomatic	Should continue pembrolizumab with monitoring of TSH (option for FT4) every 4-6 weeks as part of routine care.
G2: Moderate symptoms, able to perform ADL; TSH persistently >10 mIU/L	• May continue or hold pembrolizumab until symptoms resolve to baseline. • Consider endocrine consultation for unusual clinical presentations, concern for central hypothyroidism, or difficulty titrating hormone therapy. • Prescribe thyroid hormone supplementation in symptomatic patients with any degree of TSH elevation or in asymptomatic patients with TSH levels that persist over 10 mIU/L (measured 4 weeks apart). • Monitor TSH every 6-8 weeks while titrating hormone replacement to goal of TSH within the reference range.

AE and Grade by CTCAE v5.0	Management
	• FT4 can be used to help interpret ongoing abnormal TSH levels on therapy, as TSH may take longer to normalize. • Once adequately treated, repeat testing every 6-12 months or as indicated for a change in symptoms.
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	• Hold pembrolizumab until symptoms resolve to baseline with appropriate supplementation • Endocrine consultation to assist with rapid hormone replacement. • Hospital admission for developing myxedema (bradycardia, hypothermia, altered mental status). • Inpatient endocrinology consultation can assist with IV levothyroxine dosing, steroids, and supportive care. • If there is uncertainty about whether primary or central hypothyroidism is present, hydrocortisone should be given before thyroid hormone is initiated. • Myxedema coma is a life-threatening emergency requiring admission and a high level of care. • Thyroid supplementation and reassessment as in G2.
Thyrotoxicosis	
G1: Asymptomatic or mild symptoms	• Can continue pembrolizumab. • Beta-blocker (e.g., atenolol or propranolol) for symptomatic relief. • Close monitoring of thyroid function every 2-3 weeks after diagnosis to catch the transition to hypothyroidism, the most common outcome for transient subacute thyroiditis. • Treat transition to elevated TSH and low FT4 as for primary hypothyroidism. • For persistent thyrotoxicosis (>6 weeks) consider endocrine consultation for additional work up.
G2: Moderate symptoms, able to perform ADL	• Consider holding pembrolizumab until symptoms return to baseline. • Consider endocrine consultation. • Beta-blocker (e.g., atenolol or propranolol) for symptomatic relief. • Hydration and supportive care. • For persistent thyrotoxicosis (>6 weeks) refer to endocrinology for additional workup and possible medical thyroid suppression.
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	• Hold pembrolizumab until symptoms resolve to baseline with appropriate therapy. • Endocrine consultation for all patients. • Beta-blocker (e.g., atenolol or propranolol). • Hydration and supportive care. • Consider hospitalizing patients in severe cases as in-patient endocrine consultation can guide the use of additional medical

AE and Grade by CTCAE v5.0	Management
	therapies including steroids, potassium iodide (SSKI), or thionamide (methimazole or propylthiouracil) and possible surgery.
Adrenal	
Primary AI	
G1: Asymptomatic or mild symptoms	• Consider holding pembrolizumab until patient is stabilized on replacement hormone. • Endocrine consultation. • Initiate replacement therapy with hydrocortisone (15-20 mg in divided dose). • Titrate hydrocortisone to maximum of 30 mg daily total dose for residual symptoms of AI. • Reduce maintenance dosing for symptoms of iatrogenic Cushing's syndrome (e.g., bruising, thin skin, edema, weight gain, hypertension, and hyperglycemia). • Most primary AI will also require fludrocortisone (starting dose 0.5-0.1 mg/d). Adjust based on volume status, sodium level, and renin response (target upper half of the reference range).
G2: Moderate symptoms, able to perform ADL	• Consider holding pembrolizumab until patient is stabilized on replacement hormone. • Endocrine consultation. • See in clinic to assess need for hydration, supportive care, and hospitalization. • Initiate outpatient corticosteroid treatment at 2-3 times maintenance (e.g., hydrocortisone 30-50 mg total dose or prednisone 20 mg daily) to manage acute symptoms. • Initiate fludrocortisone (0.5-0.1 mg/d). • Decrease stress dose corticosteroids down to maintenance doses after 2 days. • Maintenance therapy as in G1.

G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	• Hold pembrolizumab until patient is stabilized on replacement hormone.
	• Endocrine consultation.
	• Inpatient management may be needed to provide:
	  • Normal saline (at least 2 L).
	  • IV Stress dose steroids: Hydrocortisone 50-100 mg Q6-8 hours initial dosing.
	• Taper stress dose corticosteroids down to oral maintenance doses over 5-7 days.
	• Maintenance therapy as in G1.

AE and Grade by CTCAE v5.0	Management
Pituitary	
Hypophysitis	
G1: Asymptomatic or mild symptoms	• Consider holding pembrolizumab until patient is stabilized on replacement hormones. • Endocrine consultation. • Corticosteroid replacement for AI with preference for hydrocortisone (15-20 mg in divided doses). • Initiate other hormone replacement only after any needed adrenal replacement to avoid precipitating adrenal crisis. • Thyroid hormone replacement if needed using dosing as above for primary hypothyroidism, with a goal FT4 in the upper half of the reference range (TSH is not accurate in central hypothyroidism). • Testosterone or estrogen therapy if needed in those without contraindications (e.g., prostate cancer, breast cancer, or history of DVT). • Recommend education on stress dosing, emergency injectable, and a medical alert or necklace accessory or system
G2: Moderate symptoms, able to perform ADL	• Consider holding pembrolizumab until patient is stabilized on replacement hormones • Endocrine consultation. • Clinic evaluation to assess need for steroids and volume repletion. • Consider oral pulse dose therapy in patients with MRI findings of swelling or threatened optic chiasm compression (prednisone 1 mg/kg/d [or equivalent]). Taper over 1-2 weeks and transition to physiologic maintenance therapy once down to 5 mg prednisone equivalent. • Hormonal supplementation as in G1.

AE and Grade by CTCAE v5.0	Management

G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	• Hold pembrolizumab until patient is stabilized on replacement hormones.
	• Endocrine consultation.
	• Hospitalize or make an ED referral for:
	  • Normal saline (at least 2 L) or monitored free water replacement if DI.
	  • IV Stress dose steroids: Hydrocortisone 50-100 mg Q6-8 hours initial dosing.
	  • Oral pulse dose therapy with prednisone 1-2 mg/kg daily (or equivalent) tapered over at least 1-2 weeks to physiologic maintenance in patients with significant swelling on MRI, optic chiasm compression, severe headache, or visual changes.
	• Taper stress dose corticosteroids down to oral maintenance doses over 5-7 days.
	• Maintenance therapy as in G1.

Diabetes	

G1: Asymptomatic or mild symptoms; T2DM with fasting glucose value > ULN to 160 mg/dL (> ULN to 8.9 mmol/L). No evidence of CIADM such as ketoacidosis or laboratory evidence of pancreatic autoimmunity	• Can continue pembrolizumab with close clinical follow-up and laboratory evaluation.
	• Refer to PCP for additional management or:
	  • May initiate oral therapy for those with new onset T2DM.
	  • Intensify medical therapy for those with worsening T2DM.

G2: Moderate symptoms, able to perform ADL; T2DM with fasting glucose value >160 to 250 mg/dL (>8.9 to 13.9 mmol/L). No ketoacidosis or metabolic derangements but other evidence of CIADM at any glucose level.	• May hold pembrolizumab until glucose control is obtained. • Urgent endocrine consultation for any patient with new-onset CIADM. • Initiate insulin for CIADM (or as default therapy if there is any question about the diagnosis). • Referral to ED or hospital admission if unable to initiate therapy, urgent outpatient specialist evaluation is not available, developing ketoacidosis or other concern for CIADM.
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL; G3: >250-500 mg/dL (>13.9-27.8 mmol/L); G4: >500 mg/dL (>27.8 mmol/L).	• Hold pembrolizumab until glucose control is obtained with reduction of toxicity to ≤G1. • Admit for inpatient management of DKA, volume and electrolyte resuscitation, and insulin initiation. • Endocrine consultation for all patients. • Insulin therapy appropriate for all patients.

AE and Grade by CTCAE v5.0	Management
Ketoacidosis or other metabolic abnormality.	
Musculoskeletal Toxicities	
Inflammatory Arthritis	
G1: Mild pain with inflammation, erythema, or joint swelling	• Continue pembrolizumab. • Initiate analgesia with acetaminophen and/or NSAIDs.
G2: Moderate pain associated with signs of inflammation, erythema, or joint swelling; limiting instrumental ADL	• Consider holding pembrolizumab. • Escalate analgesia and consider higher doses of NSAIDs as needed. • If inadequately controlled, initiate prednisone 10-20 mg/d or equivalent. • If improvement, slow taper according to response during the next 4-6 weeks. If no improvement after initial 4 weeks, treat as G3. • If unable to lower corticosteroid dose to below 10 mg/d after 6-8 weeks, consider DMARD. • Consider intra-articular steroid injections for large joints. • Referral to rheumatology.
G3-4: Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; limiting self-care ADL	• Hold pembrolizumab temporarily and may resume in consultation with rheumatology, if recover to ≤G1. • Initiate oral prednisone 0.5-1 mg/kg. • If failure of improvement after 2 weeks or worsening in meantime, consider synthetic or biologic DMARD. • Synthetic: methotrexate, leflunomide, hydroxychloroquine, sulfasalazine alone or in combination. • Biologic: Consider anti-cytokine therapy such as TNFα or IL-6 antagonists. Note: As a caution, IL-6 inhibition can cause intestinal perforation. While this is extremely rare, it should not be used in patients with concomitant immune-related colitis. • Referral to rheumatology.
Myositis	
G1: Mild weakness with or without pain	• Continue pembrolizumab. • If CK and/or aldolase are elevated and patient has muscle weakness may offer oral corticosteroids, starting prednisone at 0.5 mg/kg/d. Offer analgesia with acetaminophen or NSAIDs for myalgia if there are no contraindications. • Consider holding statins.

AE and Grade by CTCAE v5.0	Management
G2: Moderate weakness with or without pain limiting age-appropriate instrumental ADL	• Hold pembrolizumab temporarily and may resume upon symptom control, if CK is normal and prednisone dose <10 mg; if worsens, treat as per G3. • NSAIDs as needed. • Referral to rheumatologist or neurologist. • If CK is elevated (×3 ULN or more), initiate prednisone or equivalent at 0.5-1 mg/kg/d • May require permanent discontinuation of pembrolizumab in cases with G2 symptoms if patient had other objective findings of severe muscle involvement such as very elevated enzymes, or extensive involvement as determined by EMG, MRI, or histology • Pembrolizumab should not be restarted until CK is normal and clinical manifestations of myositis are resolved.
G3-4: Severe weakness with or without pain; limiting self-care ADL	• Hold pembrolizumab. • Consider hospitalization for patients with severe weakness severely limiting mobility, respiratory, dysphagia, or rhabdomyolysis. • Urgent referral to rheumatologist and/or neurologist. • Initiate prednisone 1 mg/kg/d or equivalent. • For patients with severe compromise, start 1-2 mg/kg of methylprednisolone IV or higher dose bolus. • Consider plasmapheresis in patients with acute/severe disease as guided by rheumatology/neurology. • Consider IVIG therapy, noting onset of action is slower. Note: Plasmapheresis immediately after IVIG will remove immunoglobulin. • Consider other immunosuppressant therapy including biologics (e.g., rituximab), TNFα, or IL-6 antagonists if symptoms worsen or if no improvement after 2 weeks. Other synthetic immunosuppressants such as methotrexate, azathioprine, or MMF could be considered for maintenance, or if symptoms and CK levels do not resolve entirely after 4 weeks. Rituximab is used in primary myositis. • Consider permanent discontinuation of pembrolizumab.
Polymyalgia-Like Syndrome	
G1: Mild stiffness and pain	• Continue pembrolizumab. • Initiate analgesia with acetaminophen and/or NSAIDs if there are no contraindications.
G2: Moderate stiffness and pain; limiting age	• Consider holding pembrolizumab and resuming upon symptom control, prednisone <10 mg; if worsens, treat as per G3.

AE and Grade by CTCAE v5.0	Management
appropriate instrumental ADL	• Initiate prednisone 20 mg/d or equivalent. If symptoms improve, start to taper dose after 3-4 weeks. • If no improvement or need for higher dosages after 4 weeks, escalate to G3. • Consider referral to rheumatology.
G3-4: Severe stiffness and pain; limiting self-care ADL	• Hold pembrolizumab and may resume, in consultation with rheumatology, if recover to ≤G2. However, note that cases of toxicity returning upon rechallenge have been reported. • Referral to rheumatology. • Should initiate prednisone 40 mg/d or equivalent. If no improvement or need for higher dosages for prolonged time, may offer a steroid sparing agent such as synthetic drugs (e.g., methotrexate) or biologic agents (e.g., IL-6 antagonists). Note: As caution, IL-6 inhibition can cause intestinal perforation. While this is extremely rare, it should not be used in patients with immune-related colitis. • Consider admission of patients with severe symptoms.
Renal Toxicities	
Nephritis or Acute Kidney Injury	
G1: Creatinine level increase of >0.3 mg/dL; creatinine 1.5-2.0× above baseline	Consider temporarily holding pembrolizumab and/or other potential contributing agents in combination regimens, pending consideration of potential alternative etiologies (recent IV contrast, medications, fluid status, UTI) and baseline renal function. A change that is still <1.5 ULN could be meaningful.
G2: Creatinine 2-3× above baseline	• Hold pembrolizumab temporarily. • Consult nephrology. • Evaluate for other causes (recent IV contrast, medications, fluid status, etc.) If other etiologies are ruled out, administer 0.5-1 mg/kg/d prednisone equivalents. • If worsening or no improvement after 1 week, increase to 1-2 mg/kg/d prednisone equivalents and permanently discontinue pembrolizumab. • If improved to ≤G1, taper steroids over at least 4 weeks. • If no recurrence of CRI, discuss resumption of pembrolizumab with patient after taking into account the risks and benefits. Resumption of pembrolizumab can be considered once steroids have been successfully tapered to ≤10 mg/d or discontinued.
G3: Creatinine >3× baseline or >4.0 mg/dL; hospitalization indicated	• Permanently discontinue pembrolizumab if it is directly implicated in renal toxicity. • Consult nephrology.

AE and Grade by CTCAE v5.0	Management
G4: Life-threatening consequences; dialysis indicated; creatinine 6× above baseline	• Evaluate for other causes (recent IV contrast, medications, fluid status, UTI, etc.). • Administer corticosteroids (initial dose of 1-2 mg/kg/d prednisone or equivalent).
Nephritis or Acute Kidney Injury – Follow-up	
G1: Creatinine level increase of >0.3 mg/dL; creatinine 1.5-2.0× above baseline	• If improved to baseline: • Resume routine creatinine monitoring.
G2: Creatinine 2-3× above baseline	• If improved to G1: • Taper corticosteroids over at least 4 weeks before resuming treatment with routine creatinine monitoring. • If elevations persist >7 days or worsen and no other cause found, treat as G3.
G3: Creatinine >3× baseline or >4.0 mg/dL; hospitalization indicated	• If improved to G1: • Taper corticosteroids over at least 4 weeks. • If elevations persist >3-5 days or worsen, consider additional immunosuppression (e.g., infliximab, azathioprine, cyclophosphamide [monthly], cyclosporine, mycophenolate).
G4: Life-threatening consequences; dialysis indicated; creatinine 6× above baseline	• If improved to G1: • Taper corticosteroids over at least 4 weeks. • If elevations persist >2-3 days or worsen, consider additional immunosuppression (e.g., infliximab, azathioprine, cyclophosphamide [monthly], cyclosporine, mycophenolate).

AE and Grade by CTCAE v5.0	Management
Nervous System Toxicities	
Myasthenia Gravis	
No G1	NA
G2: Some symptoms interfering with ADLs. MGFA severity class I (ocular symptoms and findings only) and MGFA severity class II (mild generalized weakness).	• Hold pembrolizumab and may resume in G2 patients (MGFA 1 and 2) only if symptoms resolve and steroid taper completed. • Neurology consultation. • Strongly consider in-patient care as patients can deteriorate quickly. • Pyridostigmine starting at 30 mg oral three times a day and gradually increase to maximum of 120 mg oral four times a day as tolerated and based on symptoms and wean based on improvement. These procedures should be done in close collaboration with the neurologist. • Administer corticosteroids (prednisone 0.5 mg/kg orally daily). Wean based on symptom improvement.
G3-4: Limiting self-care and aids warranted, weakness limiting walking, ANY dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms or MGFA severity class III-V (moderate to severe generalized weakness to myasthenic crisis)	• Follow G2 recommendations as listed, with the following additions for G3-4: • Permanently discontinue pembrolizumab. • Admit patient, may need ICU-level monitoring. • Continue steroids, taper should begin 3-4 weeks after initiation then wean based on symptom improvement. • Initiate IVIG 2 g/kg IV over 5 days (0.4 g/kg/d) or plasmapheresis × 5 days. • Consider adding rituximab if refractory to IVIG or plasmapheresis. • Frequent pulmonary function assessment. • Daily neurologic review.
GBS	
No G1	NA
G2: Moderate: some interference with ADLs, symptoms concerning to patient. G3-4: Severe: limiting self-care and aids warranted, weakness limiting walking, ANY dysphagia, facial weakness, respiratory muscle weakness, or	• Discontinue pembrolizumab. • Neurology consultation. • Admission to inpatient unit with capability of rapid transfer to ICU-level monitoring. • Start IVIG (0.4 g/kg/d for 5 days for a total dose of 2 g/kg) or plasmapheresis. Note: plasmapheresis immediately after IVIG will remove immunoglobulin. • Corticosteroids are usually not recommended for idiopathic GBS; however, in pembrolizumab-related forms, a trial is reasonable (methylprednisolone 2-4 mg/kg/d), followed by slow steroid taper. Pulse steroid dosing (methylprednisolone 1 g daily for 5 days) may

AE and Grade by CTCAE v5.0	Management
rapidly progressive symptoms.	also be considered for G3-4 along with IVIG or plasmapheresis. After pulse steroids, taper steroids over 4-6 weeks. • Frequent neuro checks and pulmonary function monitoring. • Monitor for concurrent autonomic dysfunction. • Non-opioid management of neuropathic pain, for example, pregabalin, gabapentin, or duloxetine. • Treatment of constipation/ileus.
Peripheral Neuropathy	
G1: Mild: no interference with function and symptoms not concerning to patient. Note: any cranial nerve problem should be managed as moderate	Low threshold to hold pembrolizumab and monitor symptoms for a week. If to continue, monitor very closely for any symptom progression.
G2: Moderate: some interference with ADLs, symptoms concerning to patient (i.e., pain but no weakness or gait limitation).	• Hold pembrolizumab and resume once return to ≤G1. • Initial observation OR initiate prednisone 0.5-1 mg/kg/d (if progressing from mild). • Gabapentin, pregabalin, or duloxetine for pain.
G3-4: Severe: limiting self-care and aids warranted, weakness limiting walking or respiratory problems (i.e., leg weakness, foot drop, rapidly ascending sensory changes). Severe may be GBS and should be managed as such.	• Permanently discontinue pembrolizumab. • Admit patient. • Neurology consultation. • Initiate IV methylprednisolone 2-4 mg/kg/d and proceed as per GBS management.
Autonomic Neuropathy	
G1: Mild: no interference with function and symptoms not concerning to patient.	Low threshold to hold pembrolizumab and monitor symptoms for a week. If to continue, monitor very closely for any symptom progression.
G2: Moderate: some interference with ADLs, symptoms concerning to patient.	• Hold pembrolizumab and resume once return to ≤G1 and off prednisone if used. • Initial observation OR initiate prednisone 0.5-1 mg/kg/d (if progressing from mild). • Neurology consultation.

AE and Grade by CTCAE v5.0	Management
G3-4: Severe: limiting self-care and aids warranted.	• Permanently discontinue pembrolizumab. • Admit patient. • Initiate methylprednisolone 1 g daily × 3 days followed by oral steroid taper. • Neurology consultation.
Aseptic Meningitis	
G1: Mild: no interference with function and symptoms not concerning to patient. Note: any cranial nerve problem should be managed as moderate. G2: Moderate: some interference with ADLs, symptoms concerning to patient (i.e., pain but no weakness or gait limitation). G3-4: Severe: limiting self-care and aids warranted	• Hold pembrolizumab and discuss resumption with patient only after taking into account the risks and benefits. • Consider neurology consult. • Consider empiric antiviral (IV acyclovir) and antibacterial therapy until CSF results. • Once bacterial and viral infection negative, may closely monitor off corticosteroids or consider oral prednisone 0.5-1 mg/kg/d or IV methylprednisolone 1 mg/kg/d if moderate or severe symptoms. • Steroids can be tapered after 2-4 weeks, monitoring for symptom recurrence. • Consider hospitalization for G3-4.
Encephalitis	
G1: Mild: No interference with function and symptoms not concerning to patient. Note: any cranial nerve problem should be managed as moderate. G2: Moderate: Some interference with ADLs, symptoms concerning to patient (i.e., pain but no weakness or gait limitation). G3-4: Severe: Limiting self-care and aids warranted.	• Hold pembrolizumab and discuss resumption with patient only after taking into account the risks and benefits. • As above for aseptic meningitis suggest concurrent IV acyclovir until PCR results obtained and negative. • Trial of methylprednisolone 1-2 mg/kg/d. • Neurology consultation. • If severe or progressing symptoms or oligoclonal bands present, consider pulse corticosteroids (methylprednisolone 1 g IV daily for 3-5 days) plus IVIG 2 g/kg over 5 days (0.4 g/kg/d) or plasmapheresis. • Taper steroids following acute management over at least 4-6 weeks. • If positive for autoimmune encephalopathy or paraneoplastic antibody or limited or no improvement, consider rituximab in consultation. • Admit patient for G3-4.

AE and Grade by CTCAE v5.0	Management
Demyelinating Diseases, Including Multiple Sclerosis, Transverse Myelitis, ADEM, ON, and NMO	
G1: Asymptomatic or mild symptoms; clinical or diagnostic observations only	• Intervention not indicated. • Continue immunotherapy unless symptoms worsen or do not improve.
G2: Moderate symptoms; minimal, limiting age-appropriate instrumental ADL	• Stop pembrolizumab. • Neurology consultation. • Start prednisone 1 mg/kg daily and taper over 1 month. • Rule out infection.
G3: Severe or medically significant symptoms but not immediately life-threatening; limiting self-care ADL	• Permanently discontinue pembrolizumab. • Neurology consultation. • Non-opioid management of neuropathic pain, for example, pregabalin, gabapentin, or duloxetine. • Admit patient for methylprednisolone pulse dosing 1 g/d and consider IVIG[a] or plasmapheresis if no improvement or symptoms worsen after 3 days.
G4: Life-threatening consequences	• Permanently discontinue pembrolizumab. • Neurology consultation. • ICU level inpatient care. • Start methylprednisolone pulse dosing 1 g/d and consider IVIG or plasmapheresis if no improvement or symptoms worsen after 3 days.
Hematologic Toxicities	
Hemolytic Anemia	
G1: Hgb < LLN to 10.0 g/dL; < LLN to 6.2 mmol/L; < LLN to 100 g/L	Continue pembrolizumab with close clinical follow-up and laboratory evaluation.
G2: Hgb <10.0 to 8.0 g/dL; <6.2 to 4.9 mmol/L; <100 to 80 g/L	• Hold pembrolizumab and strongly consider permanent discontinuation. • Administer 0.5-1 mg/kg/d prednisone equivalents.

AE and Grade by CTCAE v5.0	Management
G3: Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	• Permanently discontinue pembrolizumab. • Should use clinical judgment and consider admitting the patient. • Hematology consult. • Prednisone 1-2 mg/kg/d (oral or IV equivalent depending on symptoms/speed of development). • Consider RBC transfusion per existing guidelines. Do not transfuse more than the minimum number of RBC units necessary to relieve symptoms of anemia or to return a patient to a safe Hgb range (7-8 g/dL in stable, noncardiac inpatients). • Should offer patients supplementation with folic acid 1 mg daily.
G4: Life-threatening consequences; urgent intervention indicated	• Permanently discontinue pembrolizumab. • Admit patient. • Hematology consult. • IV prednisone corticosteroids 1-2 mg/kg/d. • If no improvement on or if worsening on corticosteroids or severe symptoms on presentation, initiate other immunosuppressive drugs, such as rituximab, IVIG, cyclosporine, infliximab, MMF, or ATG. • RBC transfusion per existing guidelines. Discuss with blood bank team prior to transfusions that a patient with possible pembrolizumab SAE is in the hospital.
Acquired TTP	
G1: Evidence of RBC destruction (schistocytosis) without anemia, renal insufficiency, or thrombocytopenia clinically G2: Evidence of RBC destruction (schistocytosis) without clinical consequence with G2 anemia and thrombocytopenia	• Hold pembrolizumab and discuss resumption with patient only after taking into account the risks and benefits, noting that there are currently no data to recommend restarting pembrolizumab therapy. • Administer 0.5-1 mg/kg/d prednisone.
G3: Laboratory findings with clinical consequences (G3 thrombocytopenia, anemia, renal insufficiency >2) G4: Life-threatening consequences (e.g., CNS hemorrhage or	• Hold pembrolizumab and discuss resumption with patient only after taking into account the risks and benefits, noting that there are currently no data to recommend restarting pembrolizumab therapy. • In conjunction with hematology, initiate therapeutic PEX according to existing guidelines with further PEX dependent on clinical progress. • Administer methylprednisolone 1 g IV daily for 3 days, with the first dose typically administered immediately after the first PEX.

AE and Grade by CTCAE v5.0	Management
thrombosis/embolism or renal failure)	For patient who has an initial platelet count response, discontinue PEX. • May offer rituximab. • Consider caplacizumab if ADAMTS13 activity level is <10 IU/dL or <10% of normal, with an inhibitor or elevated anti-ADAMTS13 IgG. • If no exacerbation within 3-5 days after stopping PEX, taper steroids over 2-3 weeks, complete course of rituximab (if receiving) and discontinue caplacizumab (if receiving).
HUS	
G1-2: Evidence of RBC destruction (schistocytosis) without clinical consequences of anemia, thrombocytopenia G2	• Continue pembrolizumab with close clinical follow-up and laboratory evaluation. • Supportive care.
G3: Laboratory findings with clinical consequences (e.g., renal insufficiency and petechiae) G4: Life-threatening consequences, (e.g., CNS thrombosis or embolism or renal failure)	• Permanently discontinue pembrolizumab. • Hematology consult. • Begin therapy with eculizumab (anti-C5 antibody) 900 mg weekly × 4 doses, 1,200 mg week 5, then 1,200 mg every 2 weeks. • Red blood transfusion according to existing guidelines.
Aplastic Anemia	
G1: Mild: >0.5 PMNs × 10^9/L hypocellular marrow, with marrow cellularity <25%, Peripheral platelet count >20,000, reticulocyte count >20,000	• Hold pembrolizumab and provide growth factor support, close clinical follow-up, and laboratory evaluation. • Supportive transfusions as per local guidelines.
G2: Moderate: Hypocellular marrow <25% and two of the following ANC <500, peripheral platelet <20,000 and reticulocyte <20,000	• Hold pembrolizumab and provide growth factor support and close clinical laboratory evaluations daily. • Hematology consult. • Administer horse ATG plus cyclosporine. • Supportive transfusions as per local guidelines. All blood products should be irradiated and filtered. • HLA typing and evaluation for bone marrow transplantation if patient is a candidate.

AE and Grade by CTCAE v5.0	Management
G3-4: Severe: ANC <200, platelet count <20,000, reticulocyte count of <20,000, plus hypocellular marrow <25%.	• As per G2 • Hold pembrolizumab and monitor weekly for improvement. If not resolved, discontinue treatment until AE has reverted to G1. • If no response, repeat immunosuppression with rabbit ATG plus cyclosporine and cyclophosphamide. • For refractory patients, consider eltrombopag plus supportive care.
Lymphopenia	
All Grades	• No specific action is required for lymphopenia G1-G3 and pembrolizumab therapy should be continued. • For G4 (<250 PB lymphocyte count), continue pembrolizumab and initiate *Mycobacterium avium* complex prophylaxis and *Pneumocystis jirovecii* prophylaxis, CMV screening. HIV and hepatitis screening, if not already done. • May consider EBV testing if evidence of lymphadenopathy or hepatitis, fevers, and hemolysis occur c/w lymphoproliferative disease occurs.
ITP	
G1: Platelet count 75 to <100/μL	• Continue pembrolizumab with close clinical follow-up and laboratory evaluation.
G2: Platelet count 50 to <75/μL	• Hold pembrolizumab but monitor for improvement. If not resolved, interrupt treatment until AE has reverted to G1. • Administer prednisone 1 mg/kg per day (dosage range: 0.5–2 mg/kg per day) orally for 4 weeks followed by taper over 4-6 weeks to the lowest effective dose. • IVIG may be used in conjunction with corticosteroids if a more rapid increase in platelet count is required.
G3: Platelet count 25 to <50/μL G4: Platelet count <25/μL	• As per G2. • Hematology consult. • Consider as alternative to prednisone, dexamethasone 40 mg daily for 4 days. • If IVIG is used, the dose should initially be 1 g/kg as a one-time dose. • If previous treatment with corticosteroids and/or IVIG has been unsuccessful, subsequent treatment may include rituximab, thrombopoietin receptor agonists, or more potent immunosuppression.

AE and Grade by CTCAE v5.0	Management
Acquired Hemophilia A	
G1: Mild: 5%-40% of normal factor activity in blood; 0.05-0.4 IU/mL of whole blood	• Hold pembrolizumab and discuss resumption with patient only after taking into account the risks and benefits. • Administer 0.5-1 mg/kg/d prednisone. • Transfusion support as required. • Treatment of bleeding disorders with hematology consult.
G2: Moderate: 1%-5% of normal factor activity in blood; 0.01-0.05 IU/mL of whole blood	• Hold pembrolizumab and discuss resumption with patient only after taking into account the risks and benefits. • Administration of factor replacement (choice based on BU of titer). • Administer 1 mg/kg/d prednisone ± rituximab (dose 375 mg/m^2 weekly × 4 weeks) and/or cyclophosphamide (dose 1-2 mg/kg/d). Choice of rituximab versus cyclophosphamide is patient specific and should be done with assistance of hematology consult. Prednisone, rituximab, and cyclophosphamide should be given for at least 5 weeks. • Factors should be provided to increase level during bleeding episodes, with choice of factor based on presence or absence of inhibitor. • Transfusion support as required for bleeding.
G3-4: Severe: <1% of normal factor activity in blood; <0.01 IU/mL of whole blood	• Permanently discontinue pembrolizumab. • Admit patient. • Administration of factor replacement, choice based on BU level of inhibitor. • Bypassing agents may be used (Factor VII FEIBA). Caution should be taken in elderly patients and those with CAD. • Prednisone corticosteroids 1-2 mg/kg/d (oral or IV depending on symptoms) ± rituximab (dose 375 mg/m^2 weekly × 4 weeks) and/or cyclophosphamide (dose 1-2 mg/kg/d). • Transfusion support as required for bleeding. • If worsening or no improvement add cyclosporine or immunosuppression or immunoadsorption.

AE and Grade by CTCAE v5.0	Management
Cardiovascular Toxicities	
Myocarditis, Pericarditis, Arrhythmias, Impaired Ventricular Function with Heart Failure, and Vasculitis	
G1: Abnormal cardiac biomarker testing without symptoms and with no ECG abnormalities G2: Abnormal cardiac biomarker testing with mild symptoms or new ECG abnormalities without conduction delay G3: Abnormal cardiac biomarker testing with either moderate symptoms or new conduction delay G4: Moderate to severe decompensation, IV medication or intervention required, life-threatening conditions	• All grades warrant workup and intervention given the potential for cardiac compromise. • Hold pembrolizumab for G1 elevated troponin M and recheck troponin 6 hours later. May consider resuming once normalized or if believed not to be related to pembrolizumab. • Hold pembrolizumab and discontinue for ≥G2. • For patients with ≥G2, early (i.e., within 24 hours) initiation of high-dose corticosteroids (1-2 mg/kg/d of prednisone, oral or IV depending on symptoms) should be considered as it is likely to be beneficial without adverse effects. • Admit patient, cardiology consultation. • Management of cardiac symptoms according to ACC/AHA guidelines and with guidance from cardiology. • Immediate transfer to a coronary care unit should be considered for patients with elevated troponin or conduction abnormalities. • For new conduction delay, consider a pacemaker. • In patients without an immediate response to high-dose corticosteroids, consider early institution of cardiac transplant rejection doses of corticosteroids (methylprednisolone 1 g every day) and the addition of either mycophenolate, infliximab, or anti-thymocyte globulin. Consider abatacept (costimulatory molecule blockade) or alemtuzumab (CD52 blockade) as additional immunosuppression in life-threatening cases.
Venous Thromboembolism	
G1: Venous thrombosis (e.g., superficial thrombosis)	• Continue pembrolizumab. • Warm compress. • Clinical surveillance.

AE and Grade by CTCAE v5.0	Management
G2: Venous thrombosis (e.g., uncomplicated DVT), medical intervention indicated	• Continue pembrolizumab. • Management according to CHEST, ACC, and/or AHA guidelines and consider consult from cardiology or other relevant specialties. • LMWH, VKA, dabigatran, rivaroxaban, apixaban, or edoxaban for initial anticoagulation treatment. For long-term anticoagulation, LMWH, edoxaban, rivaroxaban, or apixaban for at least 6 months are preferred over VKAs because of improved efficacy. • IV heparin is an acceptable alternative for initial use and oral anticoagulants are acceptable for the long term.
G3: Venous thrombosis (e.g., uncomplicated pulmonary embolism), urgent medical intervention indicated	• Hold pembrolizumab and may reintroduce after risks/benefits are considered. • Follow G2 anticoagulation recommendations.
G4: Life-threatening consequences; hemodynamic or neurologic instability; organ damage; loss of extremity(ies)	• Hold pembrolizumab and may reintroduce after risks/benefits are considered. • Admit patient and management according to CHEST, ACC, and/or AHA guidelines and with guidance from cardiology. • Respiratory and hemodynamic support. • Follow G2 anticoagulation recommendations with further clinical management as indicated based on symptoms.
Ocular Toxicities	
Uveitis or Iritis	
G1: Anterior uveitis with trace cells	• Continue pembrolizumab. • Prompt referral to ophthalmology (usually within 1 week). • Artificial tears.
G2: Anterior uveitis with 1+ or 2+ cells	• Hold pembrolizumab temporarily until after ophthalmology consult. • Urgent ophthalmology referral. • Topical corticosteroids (e.g., 1% prednisolone acetate suspension), cycloplegic agents (e.g., atropine), systemic corticosteroids. • May resume pembrolizumab treatment once off systemic steroids if patient has only ocular irAE, once corticosteroids are reduced to ≤10 mg prednisone equivalent. Continued topical/ocular steroids are permitted when resuming therapy to manage and minimize local toxicity. • Retreat after return to ≤G1.

AE and Grade by CTCAE v5.0	Management
G3: Anterior uveitis with 3+ or greater cells; intermediate posterior or panuveitis	• Permanently discontinue pembrolizumab. • Urgent ophthalmology referral. • Systemic corticosteroids and intravitreal or periocular or topical corticosteroids. • Methotrexate may be used in patients who respond poorly to systemic corticosteroids or those with severe sight- threatening inflammation.
G4: Best corrected visual acuity of 20/200 or worse in the affected eye	• Permanently discontinue pembrolizumab. • Emergent ophthalmology referral. • Systemic corticosteroids - prednisone 1-2 mg/kg/d or methylprednisolone 0.8-1.6 mg/kg/d and intravitreal or periocular or topical corticosteroids per ophthalmologist opinion.
Episcleritis	
G1: Asymptomatic	• Continue pembrolizumab. • Prompt ophthalmology referral (usually within 1 week). • Artificial tears.
G2: Vision 20/40 or better	• Hold pembrolizumab temporarily until after ophthalmology consult. • Urgent ophthalmology referral. • Topical corticosteroids (e.g., 1% prednisolone acetate suspension), cycloplegic agents (e.g., atropine), systemic corticosteroids.
G3: Symptomatic and vision worse than 20/40	• Permanently discontinue pembrolizumab. • Urgent ophthalmology referral. • Systemic corticosteroids and topical corticosteroids with cycloplegic agents.
G4: 20/200 or worse	• Permanently discontinue pembrolizumab. • Emergent ophthalmology referral. • Systemic corticosteroids and topical corticosteroids with cycloplegic agents.
Systemic Toxicities	
IRRs	
G1: Mild transient reaction; infusion interruption not indicated; intervention not indicated	• Continue pembrolizumab. • May consider premedication with acetaminophen and an antihistamine for subsequent infusions.
G2: Therapy or infusion interruption indicated but responds promptly to symptomatic treatment;	• Consider holding pembrolizumab temporarily and/or reducing the rate of infusion to 50% (or per institutional guidelines). • Offer symptomatic treatment with antihistamines, NSAIDs, opioids, and IV fluids as clinically appropriate.

AE and Grade by CTCAE v5.0	Management
prophylactic medication indicated for ≤24 hours	• Offer prophylactic acetaminophen and an antihistamine per institution guidelines for subsequent infusions.
G3: Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae	• Hold pembrolizumab temporarily and consider resuming, at an infusion rate of 50% (or per institutional guidelines), once return to ≤G1. • Offer symptomatic treatment with antihistamines, NSAIDs, opioids, and IV fluids as clinically appropriate. • Consider antihistamines and corticosteroid medications intravenously. • Hospitalization for other clinical sequelae.
G4: Life-threatening consequences; urgent intervention indicated	• Permanently discontinue pembrolizumab. • ICU level inpatient care.

[a] IVIG 2 g/kg, administered in divided doses per package insert.

Abbreviations: ACC = American College of Cardiology; ADEM = acute disseminated encephalomyelitis; ADL(s) = activity(ies) of daily living; AE = adverse event; AHA = American Heart Association; AI = adrenal insufficiency; ALT = alanine aminotransferase; ANC = absolute neutrophil count; ASCO = American Society of Clinical Oncology; AST = aspartate aminotransferase; ATG = antithymocyte globulin; BAL = bronchoalveolar lavage; BSA = body surface area; BU = Bethesda units; c/w = coupled with; CAD = coronary artery disease; CD52 = cluster of differentiation 52; CHEST = American College of Chest Physicians; CIADM = checkpoint inhibitor–associated autoimmune diabetes; CK = creatine kinase; CMV = cytomegalovirus; CNS = central nervous system; CRI = chronic renal insufficiency; CSF = cerebrospinal fluid; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; CXR = chest X-ray; DI = diabetes insipidus; DIHS = drug-induced hypersensitivity syndrome; DKA = diabetic ketoacidosis; DLCO = diffusing capacity of lung for carbon monoxide; DMARD = disease-modifying anti-rheumatic drug; DRESS = drug reaction with eosinophilia and systemic symptoms; DVT = deep vein thrombosis; EBV = Epstein-Barr virus; ECG = electrocardiogram; ED = emergency department; EGD = esophagogastroduodenoscopy; EMG = electromyography; FEIBA = factor eight inhibitor bypassing activity; FT4 = free thyroxine; GBS = Guillain-Barre syndrome; GI = gastrointestinal; Gx = grade, where x is a number; Hgb = hemoglobin; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; HUS = hemolytic-uremic syndrome; ICU = intensive care unit; IgG = immunoglobulin G; IL-6 = interleukin-6; irAE = immune-related adverse event; IRR = infusion-related reaction; ITP = idiopathic thrombocytopenic purpura; IV = intravenous; IVIG = intravenous immunoglobulin; LLN = lower limit of normal; LMWH = low-molecular-weight heparin; MGFA = Myasthenia Gravis Foundation of America; MMF = mycophenolate mofetil; MRI = magnetic resonance imaging; NA = not applicable; NASH = nonalcoholic steatohepatitis; NMO = neuromyelitis optica; NSAID = non-steroidal anti-inflammatory drug; ON = optic neuritis; PB = peripheral blood; PCP = primary care practitioner; PCR = polymerase chain reaction; PEX = plasma exchange; PMN = polymorphonuclear cell; Q = every; RBC = red blood cell; SAE = serious adverse event; SCAR = severe cutaneous adverse reaction; SJS = Stevens-Johnson syndrome; SSKI = potassium iodide; T2DM = Type 2 diabetes mellitus; TEN = toxic epidermal necrolysis; TNFα = tumor necrosis factor alpha; TSH = thyroid-stimulating hormone; TTP = thrombotic thrombocytopenic purpura; ULN = upper limit of normal; UTI = urinary tract infection; VKA = vitamin K antagonist

APPENDIX 5. RECIST V. 1.1

Measurable Disease. Measurable tumor lesions (nodal, subcutaneous, lung parenchyma, solid organ metastases) are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with chest X-ray and as ≥10 mm with computed tomography (CT) scan or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥10 mm by CT scan). *Malignant lymph nodes* must be ≥15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

Non-Measurable Disease. All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin, and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

Target Lesions. When more than one measurable tumor 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 and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. Note that pathological nodes must meet the criterion of a short axis of ≥15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed. At baseline, the sum of the target lesions (longest diameter of tumor lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded. After baseline, a value should be provided on the case report form for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

Non-Target Lesions. All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered *non-target lesions*. Measurements are not required but these lesions should be noted at baseline and should be followed as “present” or “absent.”

Response.

All patients will have their BEST OBJECTIVE RESPONSE from the start of study treatment until the end of treatment classified as outlined below:

Complete Response (CR): disappearance of target and non-target lesions and normalization of tumor markers. Pathological lymph nodes must have short axis

measures <10 mm (note: continue to record the measurement even if <10 mm and considered CR). Residual lesions (other than nodes <10 mm) thought to be non-malignant should be further investigated by cytology specialized imaging or other techniques as appropriate for individual cases before CR can be accepted. Confirmation of response is required and should occur no less than 4 weeks after the initial response.

Partial Response (PR): at least a 30% decrease in the sum of measures (longest diameter for tumor lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non-target lesions must be non-PD. Confirmation of response should occur no less than 4 weeks after the initial response.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters on study.

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥5 mm. Appearance of new lesions will also constitute PD (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumor burden has increased sufficiently to merit discontinuation of treatment or where the tumor burden appears to have increased by at least 73% in volume. Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

Integration of Target, Non-Target, and New Lesions into Response Assessment

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for This Category Also Requires
Target lesions ± non-target lesions				
CR	CR	No	CR	Normalization of tumor markers, tumor nodes <10 mm
CR	Non-CR/Non-PD	No	PR	
CR	Not all evaluated	No	PR	
PR	Non-PD/not all evaluated	No	PR	
SD	Non-PD/not all evaluated	No	SD	Documented at least once ≥4 wks. from baseline
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
Non-target lesions ONLY				
No target	CR	No	CR	Normalization of tumor markers, tumor nodes <10 mm
No target	Non-CR/non-PD	No	Non-CR/non-PD	
No target	Not all evaluated	No	NE	

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for This Category Also Requires
No target	Unequivocal PD	Any	PD	
No target	Any	Yes*	PD	

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.
*Investigators should record all new lesions; if the new lesion is felt to be equivocal, treatment may be continued pending further assessments.
Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.